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Study of Some Selective Reductions of 4-Androstene-3,11,17-Trione

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Northern Michigan University

A STUDY OF SOME SELECTIVE REDUCTIONS OF 4-ANDROSTENE-3,11,17-TRIONE

by

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B. S., NORTHERN MICHIGAN UNIVERSITY

A Thesis

Submitted in Partial Fulfillment of the

Requirements for the Degree of

Master of Arts in Chemistry

School of Graduate Studies

Northern Michigan University

Marquette

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ABSTRACT

11α-Hydroxytestosterone, 5α-androstane-11α,17β-diol-3-one, and 5β-androstane-3α,11α,17β-triol were prepared from 4-androstene-3,11,17-trione. These steroids were made for use in radioimmunoassay procedures.

4-Androstene-3,11,17-trione was converted by ketal exchange with butanone ethylene ketal to 5-androstene-3,11,17-trione-3-ethylene ketal. This was reduced with a lithium-methanol-ammonia system to produce 11α-hydroxytestosterone ethylene ketal which was subsequently hydrolyzed to 11α-hydroxytestosterone. This was reduced with lithium in ammonia to produce androstane-11α,17β-diol-3-one.

4-Androstene-3,11,17-trione was also converted to 5β-androstane-3,11,17-trione by basic palladium in ethanol. This was followed by reduction with sodium in 1-propanol to produce 5β-androstane-3α,11α,17β-triol.

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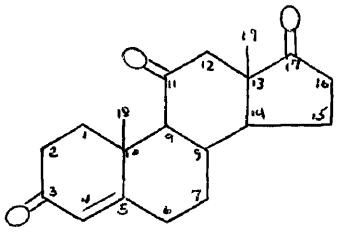
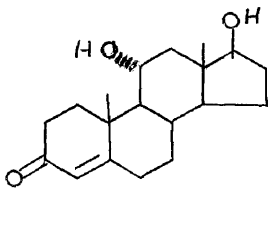
INTRODUCTION

This research dealt with the preparation of three 11α-hydroxy derivitives of 4-androstene-3,11,17-trione (I).



I

Specifically, 4-androstene-11α,17β-diol-3-one (V), 5α-androstane-11α,17β-diol-3-one (VI), and 5β-androstane-3α,-



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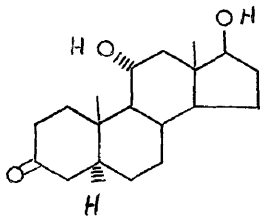

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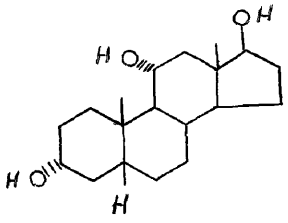

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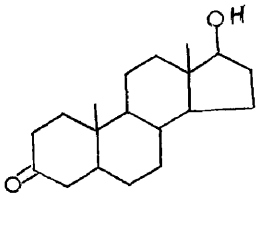

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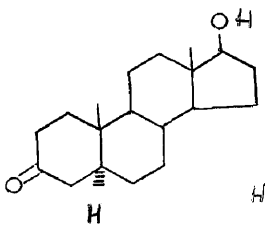

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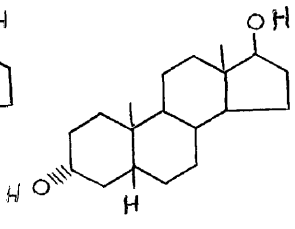


IV

11α,17β-triol (VII) were made. These compounds are of interest because of their use for the radioimmunoassay of testosterone metabolites. If the eleven hydroxyl group is ignored, these steroids correspond to testosterone (II) and two common metabolic derivitives, dihydrotestosterone (III) and 5β-androstane-3α,17β-diol (IV).

These steroids (II, III, and IV) are found in concentrations of 10^{-9} to 10^{-12} gram in the blood, concentrations much too small for conventional assay methods. Measurement of these concentrations is possible using a technique known as radioimmunoassay.[1,2,3] This method depends on an immune response between an antibody and the steroid being assayed. The antibody is usually prepared by injecting the compound under study into a rabbit and isolating the resulting antisera. A steroid is not a large enough molecule to cause the antibody response, so the steroid is attached to a larger protein molecule (usually bovine serum albumin, BSA) and the steroid-protein derivative serves as the antigen.[3]

The beta surface (top surface) of the steroid determines the specificity of the molecule towards proteins and an additional group attached to the alpha side (bottom surface) does not significantly alter the interaction between a protein and the steroid. In addition, if the alpha group is attached to the eleven or the fourteen position the substitution has an even smaller effect. Therefore, in this research 11α-hydroxy steroids were prepared.

In order to prepare a steroid-protein complex for use

in the radioimmunoassay procedure, succinic acid is attached to the 11α-hydroxy group. The free carboxylic acid group of the hemisuccinate is attached to a free amino group on bovine serum albumin (BSA) by the use of carbodiimide as the condensing reagent. The result is a steroid-protein complex, with the protein attached on the inactive alpha surface of the steroid with the beta surface still capable of interacting with other proteins (Figure 1).

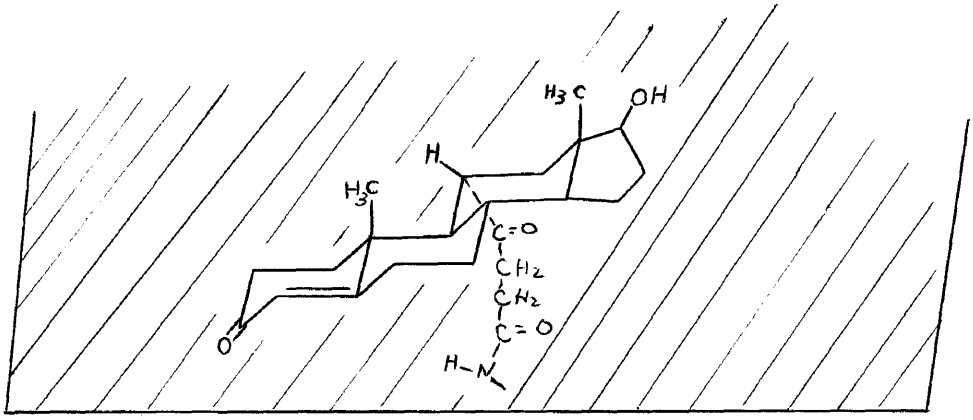


Figure 1. Steroid-BSA complex

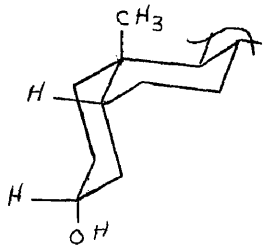
When the protein-steroid complex is injected into a rabbit, the animal's immune response system begins building antibodies to the complex. These antibodies will be specific for BSA and for the beta surface of the steroid. If 11α-hydroxytestosterone-BSA complex is used, the antisera produced will be specific for the steroid, testosterone.[3]

The starting material used for the preparation of the three compounds (VII, XII and XIV) was 4-androstene-3,11,17-trione (I). The approach to preparing the derivitives can

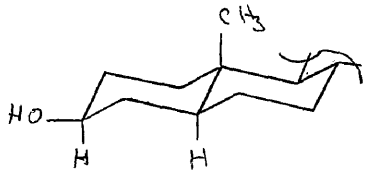
be looked at from two aspects; reduction of the carbonyl groups or reduction of the double bond.

Reduction of the carbonyl groups[4]

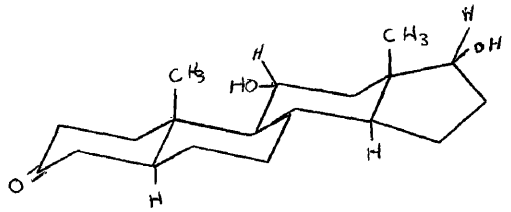
The three carbonyl groups all require stereospecific reductions. The three and eleven carbonyl groups must be reduced to the alpha isomers and the seventeenteen carbonyl group to the beta isomer. Examination of the structure of the steroids containing these three alcohols shows that each hydroxyl group is in the more stable equatorial position



5β-Androstane-3α-ol
(cis A/B ring)



5α-Androstane-3β-ol
(trans A/B ring)



5α-Androstane-11α,17β-diol-3-one

Figure 2. Steric projections for 5β-and 5α-Androstanes.

(Figure 2). When the five hydrogen is in the beta position

the A/B ring junction is cis. The alcohol group at the three position is more stable in the equatorial or alpha configuration. When the five hydrogen is alpha, the A/B ring junction is trans. In this case the equatorial alcohol is also the more stable isomer but it is in the beta configuration. Thus, any carbonyl reduction in which 4-androstene-3,11,17-trione is reduced, must take place by a method which will permit the most thermodynamically stable alcohol to form.

The method used for the carbonyl reductions was dissolving metal in alcohol. These reductions proceed by initial one electron addition to the carbonyl group to produce the radical anion or ketyl (A, Figure 3) which will assume

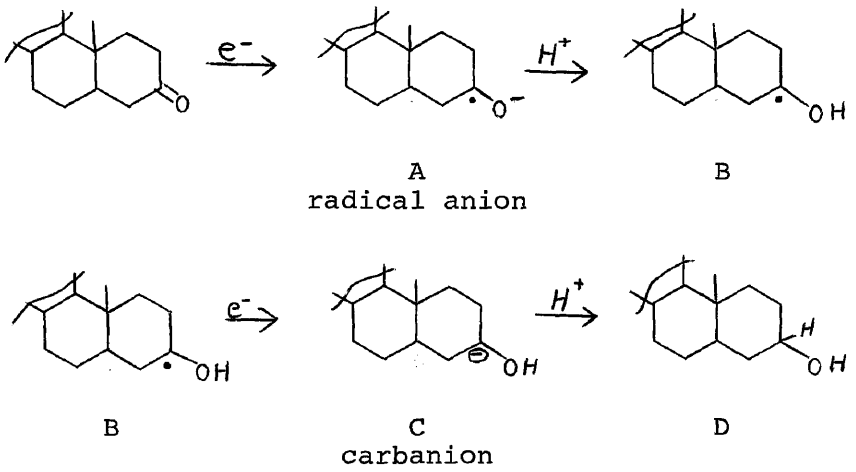


Figure 3. Mechanism for the dissolving reduction of a carbonyl group.

the most stable configuration. The anion is protonated by the alcohol solvent, (B), followed by a second electron ad-

dition to form the carbanion (C) which accepts a proton from the solvent to complete the reaction (D).[4]

Reduction of the carbon-carbon double bond

The double bond requires two different types of reductions; one in which the five beta hydrogen is the desired product and the other in which the five alpha hydrogen is the desired isomer.

Sutton has shown that reduction of an α,β-unsaturated ketone with basic palladium catalyst leads to a 100% reduction of the steroid to the 5β-hydrogen isomer[5]. Two reasons can be given to account for this specificity; the basic palladium catalyst and to a lesser extent the solvent.

In a strong basic media the α,β-unsaturated ketone will form an enolate ion (A, Figure 5). This enolate ion then becomes adsorbed on the catalyst's surface. The solvent is important because a highly polar solvent favors a 1,4 adsorption of the steroid on the catalyst's surface (Figure 4)[6,7].

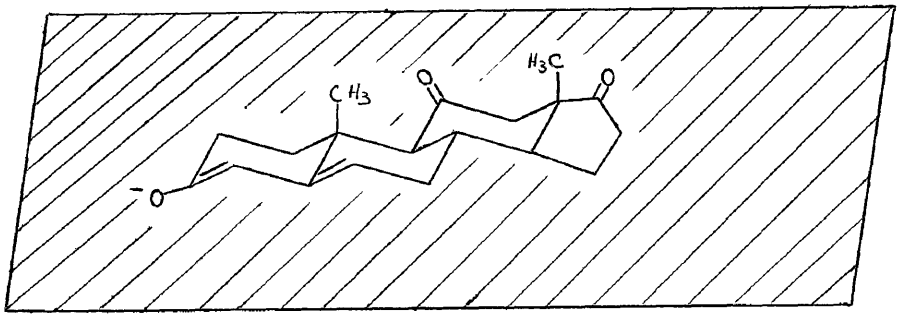


Figure 4. Adsorption of a steroid on the catalyst surface.

The polar solvent does this by polarizing the carbonyl group which aids in the trans adsorption (1,4 adsorption). The steroid molecule is rather flat and is adsorbed on the catalyst's surface along the alpha surface leaving the beta surface exposed. Adsorption on the beta side is prohibited by the beta angular methyl groups at C-10 and C-13. With the steroid adsorbed as shown in Figure 4 above, hydrogen can add to the beta or top side leading to the cis ring junction as the favored product. A non-polar solvent favors 1,2 adsorption rather than 1,4 adsorption and the product of the reduction is under less steric control and usually a 50:50 mixture of the 5α and 5β isomers is obtained.

Hydrogenation of the double bond with basic palladium as the catalyst is believed to proceed through formation of the enolate ion (A, Figure 5)[8], which is subsequently adsorbed on the surface of the catalyst (B)[9,10]. A hydride

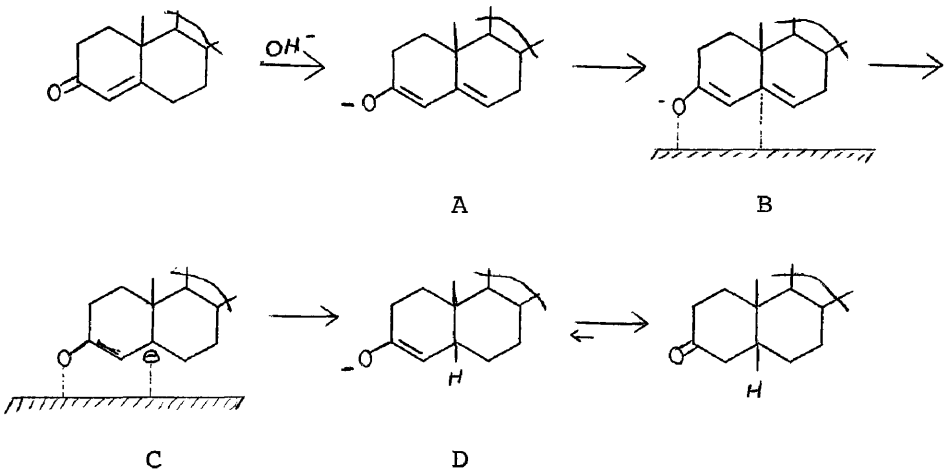
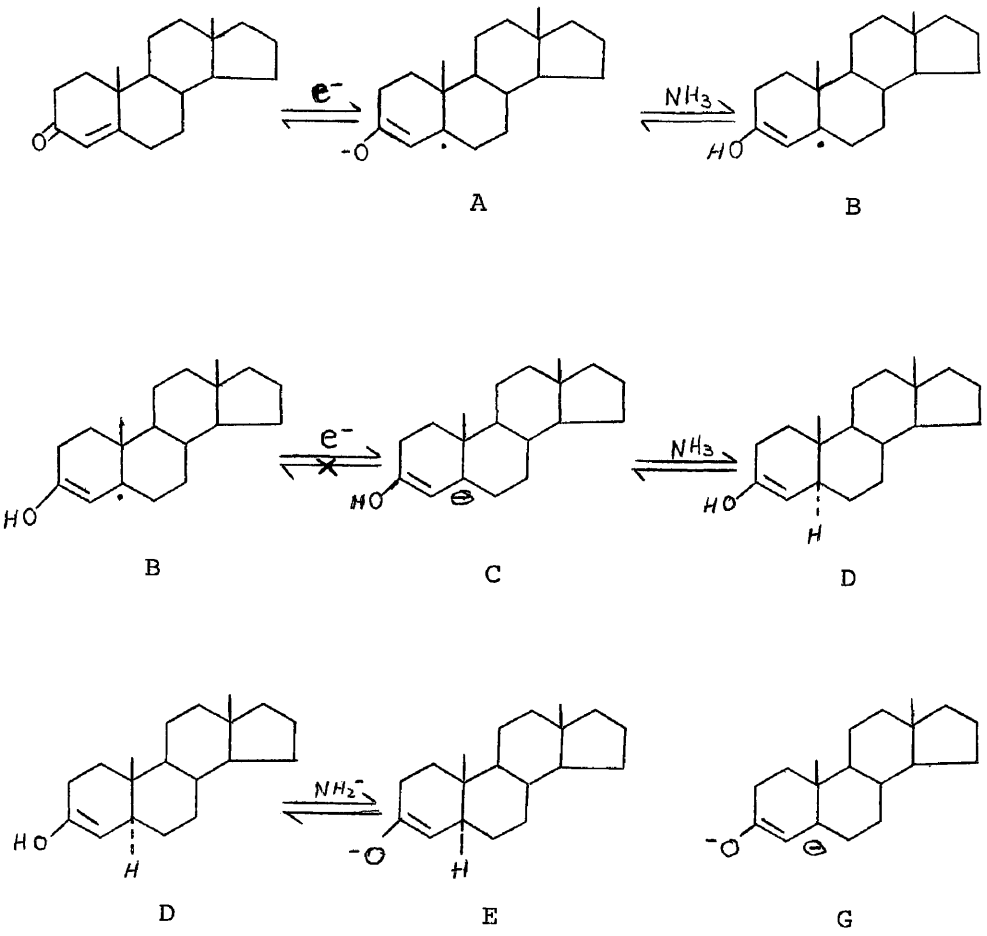


Figure 5. Mechanism of hydrogenation of a steroid using basic palladium catalyst.

ion is supplied by the catalyst to give the adsorbed dianion (C) with the steroid adsorbed on the edge opposite the angular methyl groups. The reaction goes to completion by picking up a hydrogen ion from solution.[6]

Reduction of the double bond to the 5α-isomer was carried out using lithium in liquid ammonia[11]. This reduction produces the trans A/B ring junction. The most recent and accepted mechanism for this reduction has been proposed by Bowers, Giese, Grimshaw, House, Kolodny, Kronberger and Roc[12]. They found that α,β-unsaturated ketones add an electon to produce the radical anion (A, Figure 6). This ion is protonated by the ammonia to produce the radical alcohol (B). Protonation is the second step because metal-ammonia solutions lack the reduction potential required to form the diradical (G). The equlibrium in the forward direction for this step is very small. However, the allyic radical is reduced rapidly to the carbanion (C), thus driving the forward reaction. The carbanion (C) is protonated by another ammonia molecule to form the enol (D). The alcoholic proton recombines with the amide anion to form the enolate salt (E). Isolation of the enolate salt, followed by addition of water, yields the ketone (F).

The stereochemical outcome of the reduction is determined by two factors[13]. The transition state for the reduction must have a geometry which permits the greatest over-



Removal of the ammonia, addition of water:

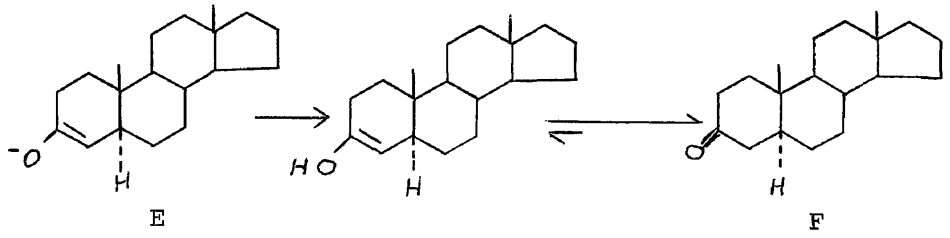


Figure 6. Mechanism of lithium-ammonia reduction of α,β-unsaturated ketone.

lap of the pi orbitals. This occurs when the rings are in the conformation shown in (A), Figure 7. The most likely conformation of the A/B ring junction during the transition state are shown in (B), (C), and (D). Of the three only the <u>trans</u> ring junction (C) will permit continuous orbital overlap in the transition state.

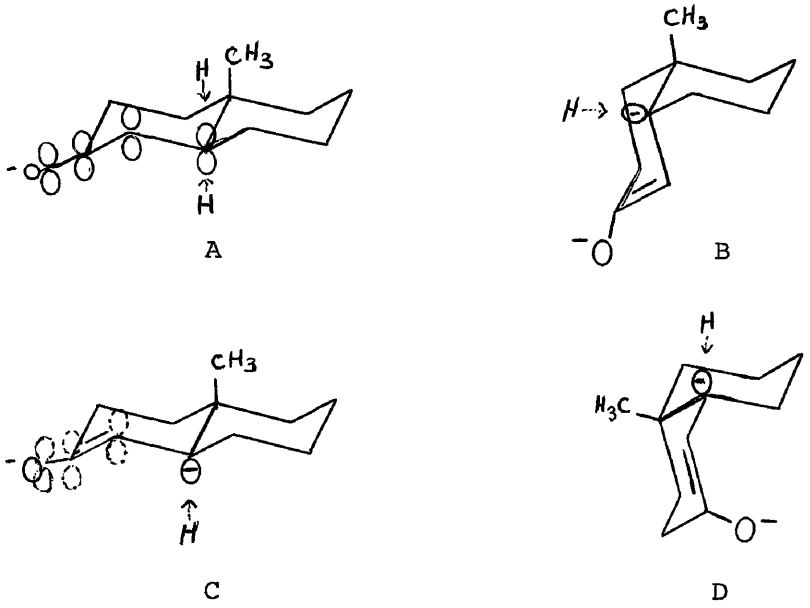


Figure 7. Stereochemical event durning metal-ammonia reduction of an α,β-unsaturated ketone

The second factor which has some influence on the steric nature of the product is the conformation of the A/B ring junction which gives the thermodynamically more stable product. In this case the <u>cis</u> ring junction is more stable because it can exist in two forms (B and D). However, the <u>cis</u> product cannot be formed because it would have to come

from a transition state which is not allowed. The steric outcome of this reduction is the trans A/B ring junction due to the orbital overlap in the transition state. [12]

A summary of the various reactions carried out in this study is given in Figure 8.

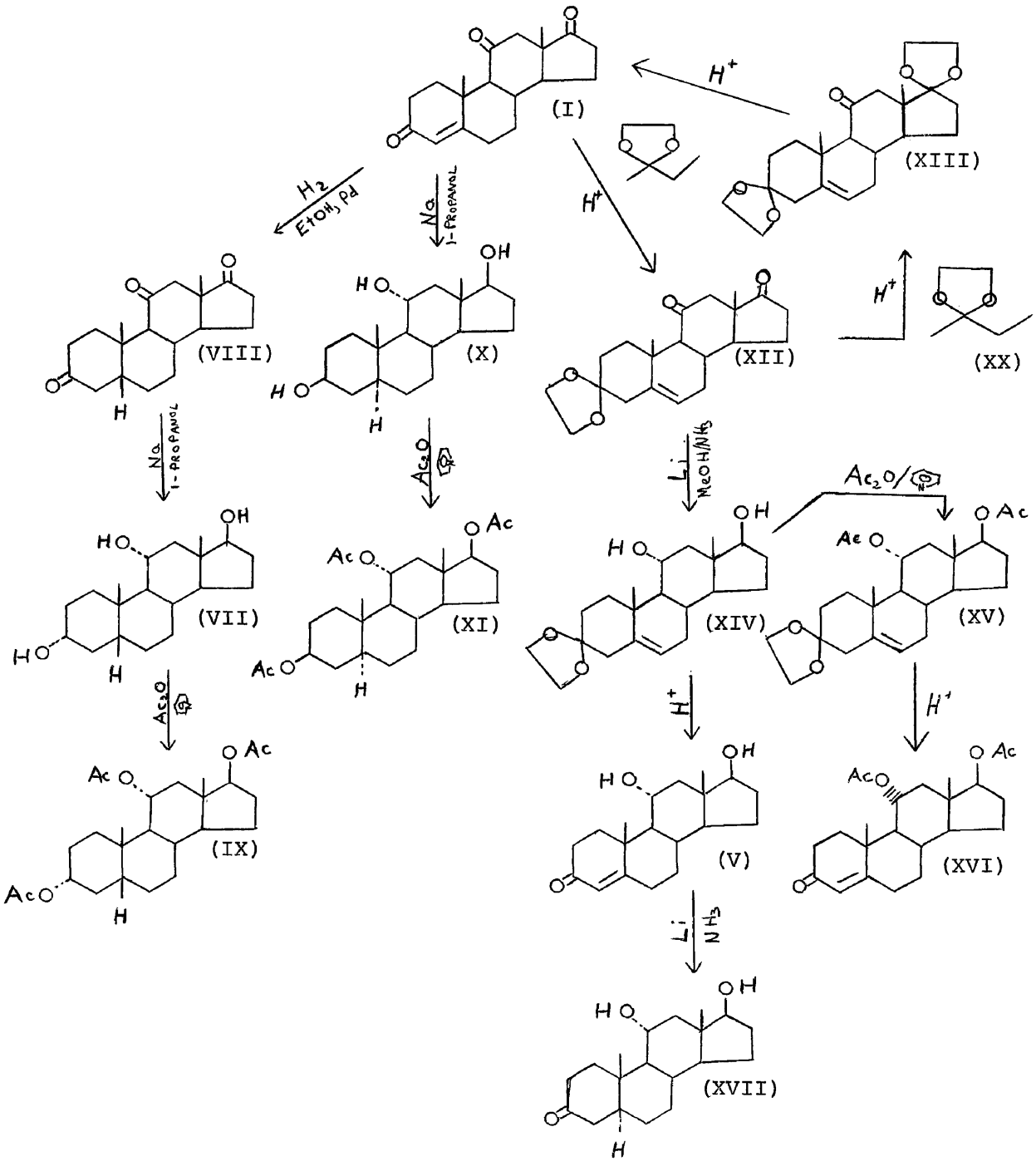


Figure 8. Summary of the various reactions carried out in this investigation.

EXPERIMENTAL

Instrumental

Infrared (IR) spectra were recorded using a Perkin-Elmer Model 337 Spectrophotometer. The samples were run as potassium bromide pellets using one milligram of sample to 150 milligrams of potassium bromide. All peaks are reported in reciprocal centimeters. The infrared spectral data were collected as a diagnostic tool only. The values reported were not corrected or compared with standard spectra. Nuclear magnetic resonance (NMR) spectra were recorded using a Varian A-60 high resolution NMR spectrometer. The solid samples were prepared as a solution of 50-300 milligrams of the sample dissolved in either chloroform-d (Norell Chemical Co., Inc., Larreling, N. J., 1% v/v tetramethylsilane, minimun isotopic purity: 99.8%) or dimethylsulfoxide-d_6 (Diaprep Inc., Aldrich Chemical Co., Inc., Milwaukee Wis., minimun isotopic purity: 99.5%). The liquid samples were run as neat solutions with tetramethylsilane as an internal reference. The chemical shifts are recorded as ppm (δ) from tetramethylsilane (TMS, δ=0.00) as an internal standard for the samples mixed with chloroform and as an external standard for the samples mixed with dimethylsulfoxide. The pressurized reductions were done in a Parr Pressure Reaction Apparatus (Parr Instrument Co., Inc., Moline Ill.). The hydrogen gas was filtered through a catalytic hydrogen purifier before it was used for the reductions. All melting points were taken

using a Fisher-Johns melting point apparatus and were corrected, using standard samples in the range of the known melting points for the sample compounds. Optical rotations were obtained using a Kern Full-Circle Polarimeter (Achaas and Co., Chicago Ill.) and a sodium light source.

Thin Layer Chromotography[14]

The thin layer separation was used for diagnostic purposes in order to determine if all of the starting material had reacted and if the reaction had yielded only one product.

Plates All plates were made using thirty five milliliters of water and fifteen grams of silica gel H for two 20 X 20 centimeter plates. Three thicknesses of masking tape were used for a thickness gauge. The plates were air dried for one-half hour, activated in an oven at 110° C. for two hours and stored in a dessicator.

Application of Steroid to the Plate The steroid was dissolved in methylene chloride and applied one centimeter from the bottom of the plate with a capillary tube. Standards as well as steroid reaction mixtures were spotted on the plates in order to permit identification of some of the reaction mixtures.

Plate Carrier Solvent A solution of methylene chloride/ethyl acetate/methyl alcohol in a volume ratio of 85/11/4 was used. The solvent mixture was permitted to reach within one centimeter of the top edge of the plate.

Plate Indicator Dye[15] A 10% (weight/volume) solution of phosphomolybdic acid in 95% ethanol was sprayed on the plate. The plate was developed in an oven at 110° C. for 5-15 minutes

PREPARATIONS

5β-Androstane-3,11,17-trione (VIII) Two grams (0.0067 moles) of 4-androstene-3,11,17-trione (I) (Sigma Chemical Co.) were dissolved in 100 ml. of absolute ethanol (Rossville Gold Shield Alcohol, reagent quality) containing 0.60 g. of potassium hydroxide, followed by the addition of 0.30 g. of 5% palladium on active carbon (Baker and Company). This mixture was placed in a pressure bottle and attached to the Parr Pressure Apparatus. The system was flushed five times with hydrogen gas and pressurized to ten psi. The reaction was carried out at 10 psi with shaking for ten minutes, during which time the pressure dropped to 5 psi. The system was repressurized to 10 psi and shaken until no additional hydrogen uptake was observed.[16] Completeness of the reaction was checked using thin layer chromotography.

The product solution was filtered through Celite and the basic filtrate neutralized to a pH of 5-6 with dilute hydrochloric acid. The solution was filtered again to remove precipitated inorganic salts, then concentrated by heating to a volume of 40 ml. Twenty milliliters of water were added and the solution was extracted with methylene chloride, dried over magnesium sulfate and evaporated to dryness giving a white foam. This residue was partially purified by boiling in petroleum ether and evaporating the portion dissolved in

the petroleum ether. A yield of 1.5 g. of partially purified product, melting point 105-120° C. (IR: Appendix 3A and 4B) was obtained. The infrared spectrum showed no carbonyl absorption due to the , -unsaturated ketone. This was the expected result because with the double bond reduced and with the three and eleven ketones both having six membered rings would have the same absorption frequency in the infrared at 1690cm^{-1}. The seventeen ketone remained unchanged at 1740cm^{-1}.

5β-Androstane-3,11,17-trione (VIII) was recovered when 200 mg. (0.00065 mole) of the partially purified product was recrystalized with ethanol and water. This gave 165 mg. (85%), melting point 135-136° C. which agrees with the literature value[17]. The infrared spectrum (Appendix 5A and 6B) gave absorptions at 2800-2995cm^{-1} (ring hydrogen-carbon stretching), 1740cm^{-1} (seventeen carbonyl group) and 1690cm^{-1} (three and eleven carbonyl groups).

5β-Androstane-3α,11α,17β-triol (VII) The general procedure for the sodium reductions was as follows: One gram (1.00 g.) of sodium was added in one portion to a refluxing mixture of 100 mg. (approximately 0.00032 mole) of the steroid ketone in 20 ml. of 1-propanol (99.9%, J. T. Baker Chem. Co., Phillipsburg, N. J.). This mixture was allowed to reflux spontaneously until the initial vigorous reaction subsided, then refluxing was maintained with a heating mantle until

sodium 1-propoxide precipitated from solution. Methanol was added to the hot mixture to dissolve the unreacted sodium and the precipitate. Twenty milliliters of water were added and the alcohol was removed by distillation until the product crystallized from solution. The cooled solution was filtered and the product recrystallized from a mixture of either methanol and water, acetone and water, or acetone and hexane. Table 1 lists the results for each of the tri-

Table 1. Yields and melting points for the formation of 5β-androstane-3α,11α,17β-triol (VII) by dissolving sodium in 1-propanol reduction.

Trial	mg. (mole) of 5β-androstane-3α,11α,17β-triol used	yield mg.	yield %	melting point
1	200 (0.00065)	60	30	240-4°C.
2	597 (0.0019)	539	94	242-4°C.
3	420 (0.0014)	395	96	241-3°C.

als. The melting points reported in the table agreed with literature values[18]. The infrared spectra gave absorption bands at 3100-3600cm^{-1} (broad hydroxyl absorption), 2800-2950cm^{-1} (carbon-hydrogen stretching of ring hydrogens), 1028, 1049 and 1073cm^{-1} (carbon-oxygen stretching of the three hydroxyl groups). No carbonyl absorption is present in the spectrum. The NMR spectrum gave singlets at δ=0.25 (3H) and δ=0.48 (3H) and a broad multiplet at δ=0.49 to

δ=3.00 (26H). No vinyl proton is present in the spectrum.

5β-Androstane-3α,11α,17β-triol triacetate (IX) The general procedure followed for all of the acetate reactions was as follows:[19] A solution of 0.5 g. (approximately 0.0017 mole) of the steroid alcohol in 10 ml. of pyridine and 3 ml. of acetic anhydride was allowed to stand overnight at room temperature. The resulting solution was diluted with hexane and washed successively with 25 ml. of ice water, 25 ml. of dilute sulfuric acid, and with 25 ml. of water. The hexane solution was dried over magnesium sulfate, evaporated and crystallized from a mixture of hexane and acetone.

When 102 mg. (0.00033 mole) of 5β-androstane-3α,11α,17β-triol was used, the crude product exhibited infrared and NMR spectra that supported the triacetate structure for the product.

The infrared spectrum gave absorptions at 2800-2985cm^{-1} (ring carbon-hydrogen stretching) and 1730cm^{-1} (ester carbonyl stretching). No hydroxyl absorption was exhibited in the spectrum. The NMR spectrum gave singlets at δ=0.84 (3H), δ=0.95 (3H), a broad multiplet at δ=1.00 to δ=1.90 (24H), and singlets at δ=1.99 (3H) and δ=2.02 (6H).

5α-Androstane-3β,11α,17β-triol (X) One gram (1.00 g. 0.0033 mole) of 4-androstene-3,11,17-trione was treated as in the preparation of IV. This gave 540 mg. (54%) of 5α-androstane-3β,11α,17β-triol, melting point 218-222° C. The infrared spectrum (Appendix 11A and 12B) gave absorption peaks

at 3100-3550cm^{-1} (broad hydroxyl absorption), 2825-2995cm^{-1} (aliphatic carbon-hydrogen stretching), 1078, 1049 and 1032cm^{-1} (carbon-oxygen stretching of the three alcohol groups). No carbonyl absorption was exhibited in the spectrum. The NMR spectrum gave a singlet at δ=0.80 (3H) and δ=1.03 (3H) and a series of peaks from δ=1.05 to δ=4.70 caused by the aliphatic ring hydrogens and the three hydroxyl groups.

5α-Androstane-3β,11α,17β-triol triacetate (XI) One hundred fifty milligrams (150 mg., 0.00045 mole) of 5α-androstane-3β,11α,17β-triol were treated as in the preparation of VIII. The crude product was diluted with chloroform-d and the NMR spectrum obtained. The NMR spectrum gave singlets at δ=0.85, δ=0.95, δ=1.98, and δ=2.02. The integral of this spectrum was not made; however by tracing the peaks and weighing the paper these four peaks are in a ratio of 1:1:1:2.

Butanone ethylene ketal (XX) A mixture of 95 ml. (1.06 moles) of butanone, 56 ml. (1.00 mole) of ethylene glycol, 0.5 g. of p-toluenesulfonic acid monohydrate, and 50 ml. of benzene were refluxed in a modified Dean-Stark trap (Figure 9). Slightly more than one mole of butanone was used to insure all of the ethylene glycol reacted. A very small excess of ethylene glycol in the product will cause the subsequent ketal exchange reaction to lose its specificity.[19] During twenty four hours, 20 ml. (1.1 moles) of water were

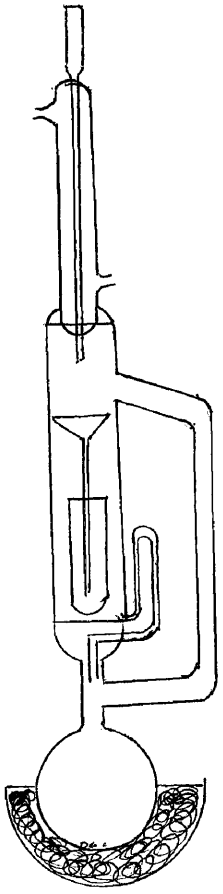


Figure 9. Modified Dean-Stark trap.

collected. The reaction was continued for a total of 48 hours. Excess sodium carbonate (two grams) was added to neutralize the p-toluenesulfonic acid. The product was fractionally distilled through a column packed with 6 mm. glass beads. The fraction distilling between 115-116° C. was collected giving 60 ml. of butanone ethylene ketal (XX). Identity of the

of the product as butanone ethylene ketal was confirmed by the boiling point of 116° C., the literature value is 115.4-116.2° C.[19] and by comparison of the NMR to the standard reference spectrum in the Sadtler table[20]. The NMR spectrum gave a triplet at δ=0.91, (3H), a singlet at δ=1.25 (3H), a quartet at δ=1.57-1.70 (2H), and a singlet at δ=3.89 (4H).

5-Androstene-3,11,17-trione-3-ethylene ketal(XII)

A mixture of 25ml (0.24 mole) of butanone ethylene ketal and one gram (1.0 g.) of lithium aluminum hydride was distilled into a 50 ml. round bottom flask, collecting 20 ml. of the distillate. If the butanone ethylene ketal was not distilled over lithium aluminum hydride, the exchange occured at both the three and the eleven positions,[21] One gram (1.00 g., 0.0033 mole) of 4-androstene-3,11,17-trione (I) and 16 mg. of p-toluenesulfonic acid monohydrate were added to the distillate. This mixture was fractionally distilled using a column packed with 6 mm. glass beads for three hours, collecting 12 ml. of distillate. The liquid remaining in the roundbottom flask was diluted with 50 ml. of benzene, then washed with a 50 ml. portion of 2.5% sodium bicarbonate followed by three washings with 50 ml. portions of water. The benzene solution was evaporated and the residue applied to a 20cm. X 1 cm. column of alumina. Elution followed by evaporation of the solvent with benzene-20%hexane gave a trace

amount of 5-androstane-3,11,17-trione-3,17-bisethylene ketal (XIII), elution with 100% benzene produced 600 mg. of the desired monoketal (5-androstane-3,11,17-trione-3-ethylene ketal (XII)), and elution with 100% methanol recovered 360 mg. of the starting material (I).

The portion collected from the benzene fraction (monoketal) was crystalized from acetone and hexane. The product melted at 190-192° C. literature 191.5° C.[22] The infrared spectrum had absorption bands at 2800-2988cm^{-1} (ring carbon-hydrogen stretching), 1730cm^{-1} (seventeen ketone), 1695cm^{-1} (eleven ketone), 1660cm^{-1} (carbon-carbon double bond), and a rather complex 'fingerprint' region. The NMR spectrum had a singlet at δ=0.86 (3H, 18-CH_3), a singlet at δ=1.25 (3H, 19-CH_3), a broad multiplet of peaks at δ=1.50 to δ=3.00 (aliphatic ring hydrogens), a sharp singlet at δ=3.96 (4H, -O-CH_2-CH_2-O-), and a broad multiplet centered at δ=5.40 (1H, vinyl proton).

Table 2 lists the six exchange reactions that were attempted and the yield of products.

5-Androstane-3,11,17-trione-3,17-bisethylene ketal (XIII)

5-Androstane-3,11,17-trione-3,17-bisethylene ketal was recovered in the column chromotography of the products of the exchange reaction described above. The yield of this product are reported on Table 2. The melting point of 184-186° C. agreed with the literature value of 184.5-186° C.[23]

Table 2.

Exchange reaction between butanone ketal and 4-androstane-3,11,17-trione (I).

Trial	g. (mole) of 4-androst-3,11,17-trione used	ml. (mole) of butanone ketal	yield (mg.)	yield (%)	product composition*
1	1.00 (0.0033)	20 (0.16)	318	25	100% C
2	0.500 (0.00017)	13 (0.10)	416	65	100% C
3	0.334 (0.00011)	16 (0.13)	235	70	40% A, 60% B
4	1.00 (0.0033)	20 (0.16)	800	72	67% B, 33% C
5	1.00 (0.0033)	10 (0.08)	1100	99	60% B, 40% C
6	2.98 (0.0098)	40 (0.32)	3347	100	40% A, 60% B

*A - 4-Androstene-3,11,17-trione (I)

B - 5-Androstene-3,11,17-trione-3-ethylene ketal (XII)

C - 5-Androstene-3,11,17-trione-3,17-bisethylene ketal (XIII)

The infrared spectrum had absorptions at 2800-3000cm^{-1} (ring carbon-hydrogen stretching), 1695cm^{-1} (eleven ketone), 1660cm^{-1} (carbon-carbon double bond), and a complex 'fingerprint' region. The NMR spectrum had sharp singlets at δ=0.83 (3H, 19-CH_3), and δ=1.23 (3H, 18-CH_3), a broad complex multiplet at δ=1.50 to δ=3.00 (aliphatic ring hydrogens), a triplet at δ=3.90, a singlet at δ=3.95 (a total of 8H, the ethylene ketals at the seventeen and three positions respectively) and a broad multiplet centered at δ=5.40 (1H, the vinyl proton).

Hydrolysis of 5-androstene-3,11,17-trione-3,17-bisethylene ketal (XIII) A mixture of 25 mg. (61 µmoles) of 5-androstene-3,11,17-trione-3,17-bisethylene ketal (XIII), 10 ml. of a 1:1 mixture of benzene and ether, and 0.10 ml. of boron trifluoride (23% in methanol) was kept at room temperature for three hours. The mixture was then washed with 35 ml. of 2.5% sodium bicarbonate followed by three 25 ml. washings of water, dried over sodium sulfate and the solvent evaporated. The infrared spectrum of the crude product was identical to the starting material, 4-androstene-3,11,17-trione (I), in every detail.

5-Androstene-11α,17β-diol-3-one-3-ethylene ketal (XIV) A solution of 620 mg. (0.0017 mole) of 5-androstene-3,11,17-trione-3-ethylene ketal (XIII) in 10 ml. of dioxane was add-

ed slowly with stirring to 123 ml. of liquid ammonia which contained 6 ml. of methanol.[24] Lithium was added slowly with stirring to the mixture until a dark blue color remained (one gram of lithium consumed). Six grams of ammonium chloride were added to destroy the remaining lithium and the ammonia was allowed to evaporate. Addition of water to the residue yielded 600 mg. of 5-androstene-11α,17β-diol-3-one-3-ethylene ketal (XIV). The product was crystallized from a mixture of hexane and acetone. The melting point of 216-218° C. agreed with the value found in literature.[25]

The infrared spectrum had absorptions at 3100-3600cm^{-1} (broad hydroxyl absorption), 1090cm^{-1} and 1135cm^{-1} (carbon-oxygen stretching of the two hydroxyl groups). No carbonyl absorption was present in the spectrum.

11α-Hydroxytestosterone (V) A solution of 238 mg. (0.00067 mole) of 5-androstene-11α,17β-diol-3-one-3-ethylene ketal (XIV), 200 mg. of p-toluenesulfonic acid monohydrate, and 100 ml. of acetone was refluxed overnight. The acetone was evaporated and the residue was crystallized from a mixture of acetone and hexane. The melting point of the product is 179-181° C. and agreed with the literature value.[25]

The infrared spectrum had absorptions at 3150-3600cm^{-1} (broad hydroxyl absorption), 2800-3000cm^{-1} (aliphatic carbon-hydrogen stretching), 1640cm^{-1} (three ketone), and 1600cm^{-1}

(carbon-carbon double bond). The NMR spectrum had singlets at δ=0.67 (19-CH_3) and δ=1.25 (18-CH_3), a complex series of peaks between δ=0.80 and δ=2.70 (aliphatic ring hydrogens), and a broad singlet at δ=5.72 (vinyl hydrogen).

5-androstene-11α,17β-diol-3-one-3-ethylene ketal diacetate (XV) Two hundred thirty one milligrams (231 mg. 0.0064 mole) of 5-androstene-11α,17β-diol-3-one-3-ethylene ketal (XIV) was treated as in the preparation of 5β-androstane-3α,11α,17β-triol triacetate (IX). This gave 239 mg. of the diacetate (XV), melting point 186-188° C. No literature value for the melting point of the diacetate was found.

The infrared spectrum had absorptions at 2800-3000cm^{-1} (aliphatic carbon-hydrogen stretching), 1730cm^{-1} (ester carbonyl group), 1030cm^{-1} and 1090cm^{-1} (carbon-oxygen stretching of ester groups). No hydroxyl absorption was present. The NMR spectrum had singlets at δ=0.94 (3H, 19-CH_3), δ=1.18 3H, 18-CH_3), δ=2.03 (3H, 17-acetate), δ=2.04 (3H, 11-acetate), δ=4.00 (4H, 3-ethylene ketal), and a multiplet at δ=5.50 (1H, vinyl proton).

4-Androstene-11α,17β-diol-3-one diacetate (XVI) A mixture of 50 mg. (110 μmoles) of 5-androstene-11α,17β-diol-3-one-3-ethylene ketal (XV), 20 mg. of p-toluenesulfonic acid monohydrate, 10 ml. of acetone, and 20 ml. of water were re-

fluxed for one hour in a 50 ml. round bottom flask. The acetone was removed by distillation and 43 g. (110 μmoles, 100%) of 4-androstene-11α,17β-diol-3-one diacetate (XVI) crystallized from the cooled solution. The melting point of 197-201° C. agreed with the literature value.[25] The infrared spectrum had absorptions at 2800-3000cm^{-1} (aliphatic carbon-hydrogen stretching), 1730cm^{-1} (ester carbonyl groups), 1655cm^{-1} (three keto group), 1600cm^{-1} (carbon-carbon double bond), and 1250cm^{-1} (carbon-oxygen stretching of the ester groups). No hydroxyl absorption was exhibited in the spectrum. The NMR spectrum had singlets at δ=0.96 (3H, 19-CH_3), δ=1.32 (3H, 18-CH_3), δ=2.08 (6H, 11,17-diacetate), δ=5.82 (1H, vinyl proton), and a broad multiplet from δ=1.40 to δ=3.00 (aliphatic ring hydrogens).

5-Androstane-11α,17β-diol-3-one (XVII) One hundred milliliters (100 ml.) of liquid ammonia were collected in a 500 ml. round bottom flask cooled in a dry ice-isopropanol bath. One gram (1.00 g.) of lithium was added in small pieces to the stirred ammonia which turned a dark blue color. A solution of 500mg. (0.0017 mole) of 11α-hydroxytestosterone (V) in 10 ml. of dioxane and 10 ml. of benzene were added slowly with stirring to the lithium and ammonia solution. The mixture was stirred for five minutes after completion of the addition, followed by the addition of 20 ml of bromobenzene to quench the lithium. Six grams (6.0 g.) of ammonium chloride

were added to the solution and the ammonia was allowed to evaporate. Addition of water yielded 500 mg. of a brown tar. The tar was crystallized from a mixture of chloroform and cyclohexane to give brown crystals, melting point 168-180° C. The infrared spectrum was identical to the starting material, 11α-hydroxytestosterone (V), in every detail.

DISCUSSION

Preparation of 5β-androstane-3α,11α,17β-triol (IV)

The sequence for the preparation and identification of 5β-androstane-3α,11α,17β-triol (VII) is shown below (Figure 10).

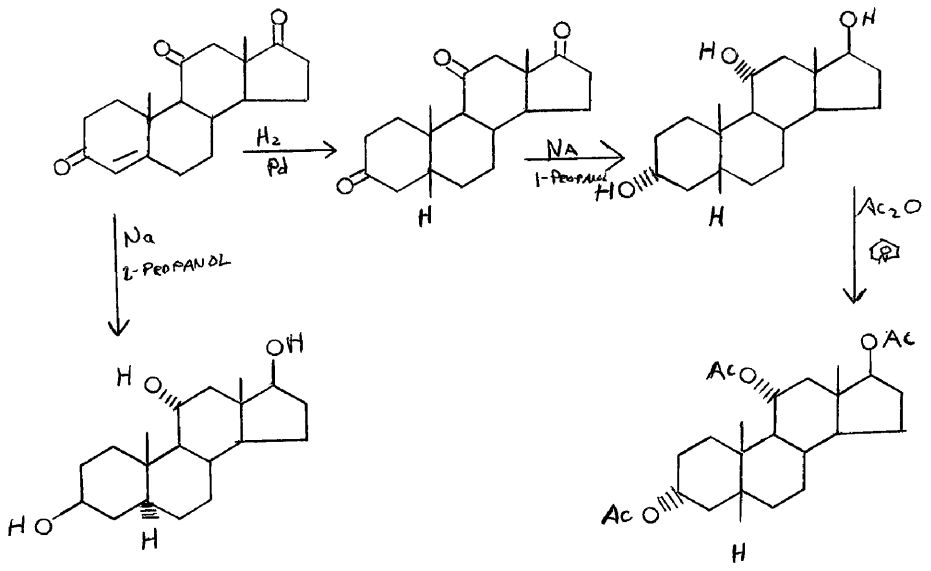


Figure 10. Sequence for the preparation and identification of 5β-androstane-3α,11α,17β-triol (VII).

The first reaction in the sequence, the palladium catalyzed reduction, caused considerable problems in attempting to purify the product, 5β-androstan-3,11,17-trione. Similar

difficulty was encountered in other laboratories as reported in literature.[17] The infrared spectrum showed a hydroxyl absorption at 3600cm^{-1} to 3100cm^{-1} indicating one or more of the carbonyl groups had been partially reduced, which caused enough impurities to be present to prevent crystallization. The hydroxyl peak also could be due to a small amount of methanol traped in the crystals. The infrared spectrum also showed two ketone peaks at 1690cm^{-1} and 1730cm^{-1}. This was the expected result, because with the double bond reduced the C-3 ketone will absorb at about the same frequency as the C-11 ketone, both being six membered alicyclic rings. One of the reduction trials did recrystallize and the melting point agreed with the value found in literature. The trials after this were unsuccessful. However, the thin layer chromotography of the reaction mixtures showed only one product present. Comparison of the infrared spectrum of the partially purified product (Appendix 3A and 4B) to that of the purified product (Appendix 5A and 6B) shows that they are essentially the same except for the presence of the hydroxyl absorption at 3600cm^{-1} to 3200cm^{-1} and the carbon-oxygen stretching peak at 1070cm^{-1}.

At this point the reaction sequence was continued without further purification of the trione. The sodium reduction produced 5 β-androstane-3 α,11 β,17 α-triol (VII), melting point 242-244° C. (literature 240-244° C.) Mixed melting point

with 5α-androstane-3β,11α,17β-trione (XI) was 190-220° C. which is lower than either the 5α- or 5β-isomer. The melting point of 5α-androstane-3β,11α,17β-trione is 228-230° C.[28] Thin layer chromotography showed only one product was formed in the sodium reduction. The optical rotation of $[\alpha]_D^{25}$ = +134.0° (0.5% in ethanol) also agrees with the literature value.[18] The optical rotation for 5α-androstane-3β,11α,17β-triol (XI) is $[\alpha]_D^{25}$ = -12° (0.5% in ethanol).[28] The infrared spectrum contained no carbonyl absorption, indicating all of the carbonyl groups were reduced.

5β-Androstane-3α,11α,17β-trione triacetate (IX) was made to confirm the production of 5β-androstane-3α,11α,17β-triol. It is impossible to produce the 11β-acetate using the method described in the experimental section.[18] This is due to the steric interference of the two beta angular methyl groups at C-10 and C-13. The two methyl groups will 'shelter' a hydroxyl groups that is in the beta position and the acetate will not be formed. The infrared spectrum of the triacetate (Appendix 9A and 10B) contains no hydroxyl absorption. The NMR of the triacetate confirmed the fact that all three acetates had been made.

Preparation of 11α-hydroxytestosterone (V)

The sequence for the preparation and identification of 11α-hydroxytestosterone (V) is shown in Figure 11. Table 3

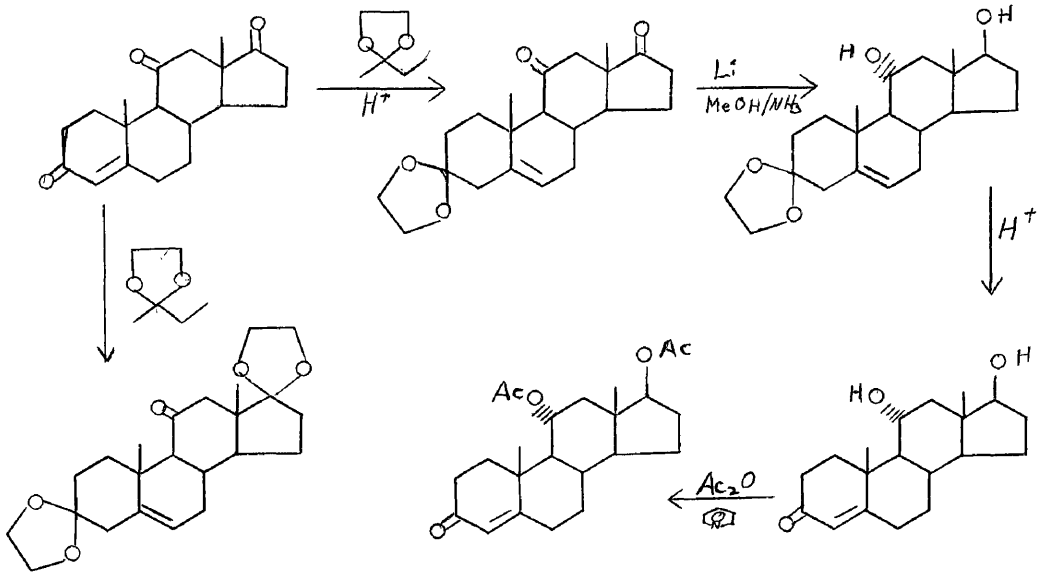


Figure 11. Sequence for the preparation and identification of 11α-hydroxytestosterone (V).

contains a list of the important infrared absorptions used to identify the various intermediates and products for all of the reaction. Table 4 contains a list of the major chemical shifts for some of the major intermediates and the products of the above sequence.

The first compound in the preparation, 5-androstene-3,11,17-trione-3-ethylene ketal (XII), was identified by the

Table 3.

Summary of the important infrared absorptions of (I), (XII), (XIII), (XIV), (V), (XV), and (XVI).

COMPOUND	Absorption peaks in cm^{-1} -C=C-	3 C=O	11 C=O	17 C=O	hydroxyl	acetate
4-Androstene-3,11,17-trione (I)	1600	1655	1690	1730		
5-Androstene-3,11,17-trione-3-ethylene ketal (XII)	1660		1690	1730		
5-Androstene-3,11,17-trione-3,17-bisethylene ketal (XIII)	1660		1690			
5-Androstene-11α,17β-diol-3-one-3-ethylene ketal (XIV)	1655				3200-3600	
11α-hydroxytestosterone (V)	1600	1655			3200-3600	
4-Androstene-11α,17β-diol-3-one diacetate (XV)	1600	1655				1730
5-Androstene-11α,17β-diol-3-one-3-ethylene ketal diacetate (XVI)						1730

Table 4.

Summary of the important chemical shifts of (I), (XII), (XIII), (V), (XV), and (XVI).

Chemical shifts in ppm.

Compound	19-CH_3	18-CH_3	3-Ketal	17-Ketal	Vinyl proton
4-Androstene-3,11,17-trione (I)	0.89	1.46			5.75
5-Androstene-3,11,17-trione-3-ethylene ketal (XII)	0.86	1.25	3.96		5.40
5-Androstene-3,11,17-trione-3,17-bisethylene ketal (XIII)	0.83	1.23	3.95	3.90	5.40
11α-hydroxytestosterone (V)	0.67	1.25			5.72
4-Androstene-11α,17β-diol-3-one diacetate (XV)	0.94	1.18	4.00		5.50
5-Androstene-11α,17β-diol-3-one-3-ethylene ketal diacetate (XVI)	0.96	1.32			5.82

melting point, and infrared and NMR spectra. The melting point of 190-192° C. agreed with the value of 191.5° C. found in literature.[22] As expected, the infrared absorption present in the starting material, (I), at 1600cm^{-1} and 1655cm^{-1} due to the α,β-unsaturated ketone were not present in the ketal's spectrum (Appendix 13A and 14B). The free eleven and seventeen ketone frequencies were exhibited in the spectrum at 1690cm^{-1} and 1730cm^{-1} respectively. The NMR spectrum (Appendix 32) of the mono ketal showed all expected peaks. The methyl protons at C-18 appeared at δ=1.25, shifted upfield δ=0.22 from occupied in the starting material. This is the type of shift expected if the ketal were formed at the three position. Ring A no longer contains the α,β-unsaturated ketone and the ketone has been converted to the ethylene ketal. Both of these factors lead to a shielding effect on the C-18 methyl protons. This also effects the C-19 methyl protons but to a much smaller extent (2 cps). The vinyl proton, δ=5.40, also experienced an upfield shift of 21 cps (δ=0.35) for the same reasons. The ethylene ketal protons occur as a sharp singlet at δ=3.96 and integrate to four protons. A mono ketal at either the eleven or the seventeen positions would occur as a multiplet due to the close proximity of the C-18 and C-19 methyl groups.

The next compound prepared, 5-androstene-e,11,17-trione-3,17-bisethylene ketal (XIII), was used to identify impurity peaks in the NMR spectra of the products of the exchange re-

actions. The melting point of 184-186° C. agreed with the value of 185-186° C. found in literature.[23] The infrared spectrum showed only the carbonyl absorption due to the C-11 keto group (1690cm^{-1}) and the carbon-carbon double bond (1660cm^{-1}) in the carbonyl region of 1600cm^{-1} to 2000cm^{-1}. The NMR spectrum exhibited all expected peaks. The positions of the C-18 and C-19 methyl protons are shifted upfield 0.9 Hz. and 1.5 Hz. respectively by the addition of the ethylene ketal in the seventeen position. The three ketal occurred as a sharp singlet at δ=3.97, approximately the same position occupied in the mono ketal. The seventeen ketal occurred as a multiplet at δ=3.95. This multiplicity is due to the close proximity of the seventeen ketal and the methyl group at C-13 (Figure 12). The ketal protons' movements are hindered cre-

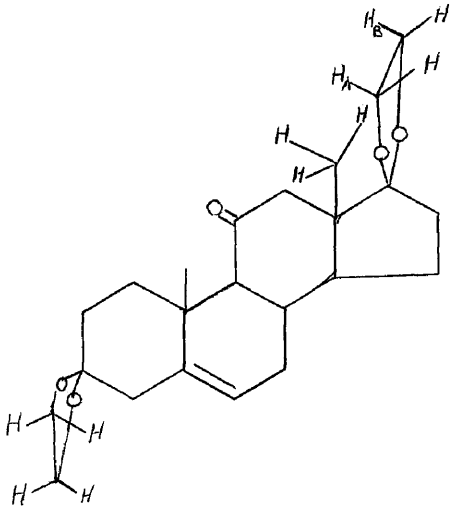


Figure 12. 5-Androstene-3,11,17-trione-3,17-bis-ethylene ketal (XIII).

ating a slightly different chemical environment for the protons (A and B) nearer the methyl protons.

The differences in the chemical shifts of the protons of the C-18 and C-19 methyl groups served as a reference point to judge the purity of the product of the exchange reactions. A small amount of one of the isomers in the product could be detected as an additional singlet near the C-18 and C-19 singlets of the major product. The infrared spectrum of the same mixture was often misleading. This can be shown by comparing the infrared spectrum of the product of one of the exchange reactions (Appendix 35A and 36B) to the NMR spectrum of the same mixture (Appendix 37). It appears from examination of the infrared spectrum that the three mono ketal was formed because both the eleven and the seventeen keto group absorptions are of equal intensity. Examination of the NMR spectrum, however, shows some of the diketal is also present; δ=0.86, C-19 of 5-androstene-3,11,17-trione-3-ethylene ketal (XII); δ=0.83, C-19 of 5-androstene-3,11,17-trione-3,17-bis-ethylene ketal (XIII).

5-Androstene-3,11,17-trione-3-ethylene ketal(XII) was converted to 5-androstene-11α,17β-diol-3-one-3-ethylene ketal (XIV) using lithium in liquid ammonia which contained methanol. The melting point of 218-220° C. agreed with the value of 216-220° C. found in literature.[25] The infrared spectrum exhibited no carbonyl absorption but did have a broad hydroxyl

absorption indicating that the two keto groups had been reduced to the alcohols.

Removal of the three ketal produced 11α-hydroxytestosterone (V). The melting point of 179-181° C. agreed with the melting point of 181° C. found in literature.[23] The 11β-hydroxytestosterone deritive melts at 235-236.5° C. The infrared spectrum showed that the ethylene ketal was removed and the α,β-unsaturated ketone peaks were present at 1600cm^{-1} and 1655cm^{-1}. The NMR showed the vinyl proton at δ=5.72 which is typical of the proton of an α,β-unsaturated ketone. If the double bond were in the five position the chemical shift would be δ=5.40.

4-Androstene-11α,17β-diol-3-one diacetate (XVI) was made to confirm the production of the 11α-acetate and 17β-acetate.[18] Production of the 11α-acetate confirms the 11α-alcohol was made.[18] The location of the C-19 methyl protons indicate the configuration of the 17-acetate group. Using the Zurcher[27] additive constants for steroids, the predicted position of the C-10 protons of the 17β-acetate is 54.4 cps and 49.5 cps for the 17α-acetate. The chemical shift found was 56 cps which is in agreement with the formation of the 17β-isomer.

Preparation of 5α-androstane-11α,17β-diol-3-one (VI)

The conversion of 11α-hydroxytestosterone (V) to 5α-androstane-11α,17β-diol-3-one (VI) was a one step process. Only enough of the starting material was made to attempt one trial of the reduction. The infrared spectrum of the product was identical to the starting material, 11α-hydroxytestosterone (V). The NMR spectrum of the product showed that a small amount of 5α-androstane-11α,17β-diol-3-one(VI) was formed. The evidence for this is the small singlet at δ=1.10 which is due to the C-18 methyl protons of 5α-androstane-11α,17β-diol-3-one. This is approximately the same position the C-18 methyl protons occur in similar systems.

A longer reaction time using some additional lithium is probably needed to complete the reaction.

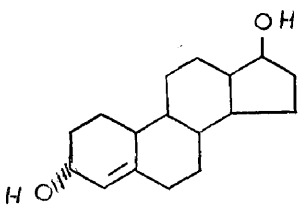
CONCLUSIONS

The methods used to prepare 11α-hydroxytestosterone (V), 5α-androstane-11α,17β-diol-3-one (VI) and 5β-androstane-3α,11α,17β-triol (VII)from commerically available 4-androstene-3,11,17-trione (I) were not found in the literature. The procedures were modifications of reactions of other steroids with similar functional groups. The preparative methods described in this investigation are useful means for making the compounds. Commercially these steroids are either unavailable or the cost is exorbitant.

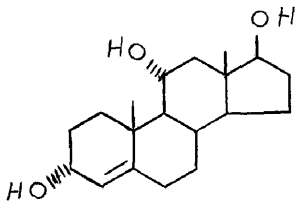
The two step procedure used to make 5β-androstane-3α,11α,17β-triol (VII) gave an overall yield of 72%. The three step procedure for 11α-hydroxytestosterone (V) gave an overall yield of 65%. In addition 30% of the starting material was recovered from the ketal exchange reaction.

Suggestions for further study

One additional derivitive of testosterone, 4-androstene-3α,17β-diol (XVIII), is also present in the blood. The 11α-hydroxy derivitive of this compound is 4-androstene-3α,11α,17β-

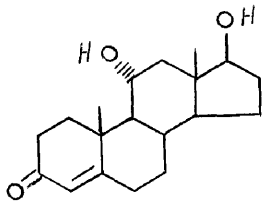


XVIII

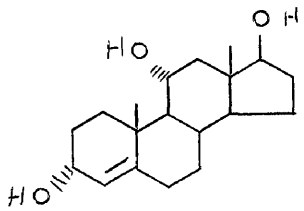


XIX

triol (XIX). This compound can be prepared by reducing the three keto group of 11α-hydroxytestosterone (V) to the three alpha alcohol derivitive (Figure 13). The dissolving metal



V



XIX

Figure 13. Preparation of 4-androstene-3α,11α,17β-triol (XIX).

reduction cannot be used to produce the more stable three alpha alcohol because these reactions will also reduce the double bond.[29] A reaction suited for this purpose is the Meerwein-Ponndrof-Verley reaction.[30,31] A detailed mechanism for this reaction is not known. However, the reduction is believed to involve a cyclic transition state[32] (Figure 14). The reaction is an equlibrium process in which the aluminum alkoxide attacks from the least hindered side of the ketone producing the least hindered alcohol.

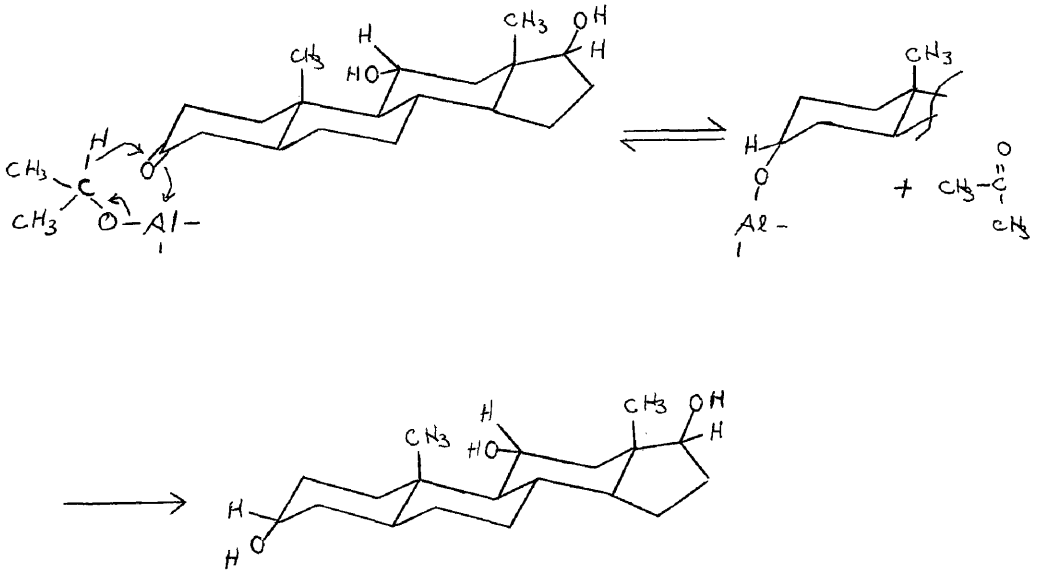


Figure 14. Mechanism for the Meerwein-Ponndrof-Verley reduction of 4-androstene-11α,17β-diol-3-one (V).

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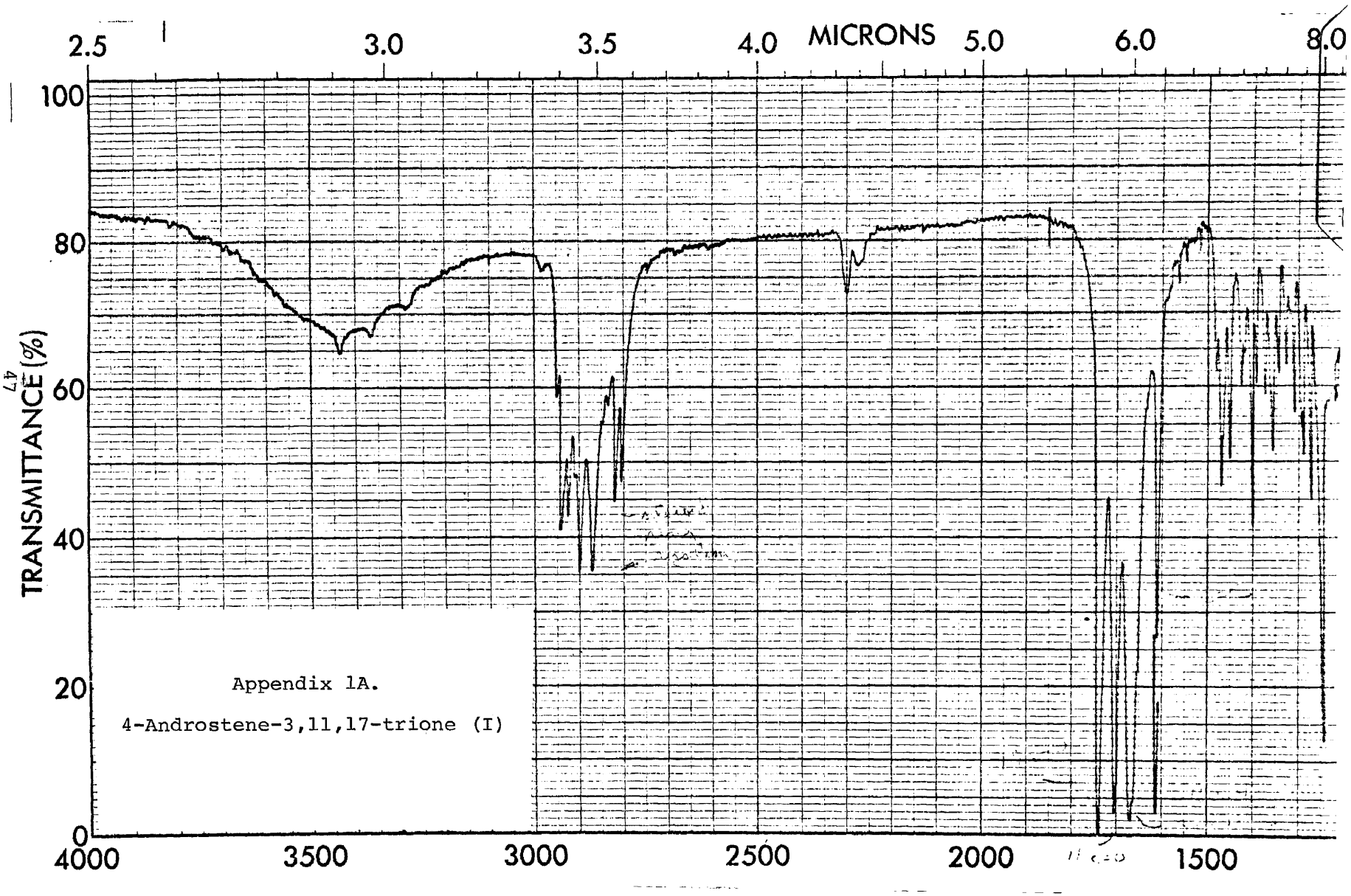
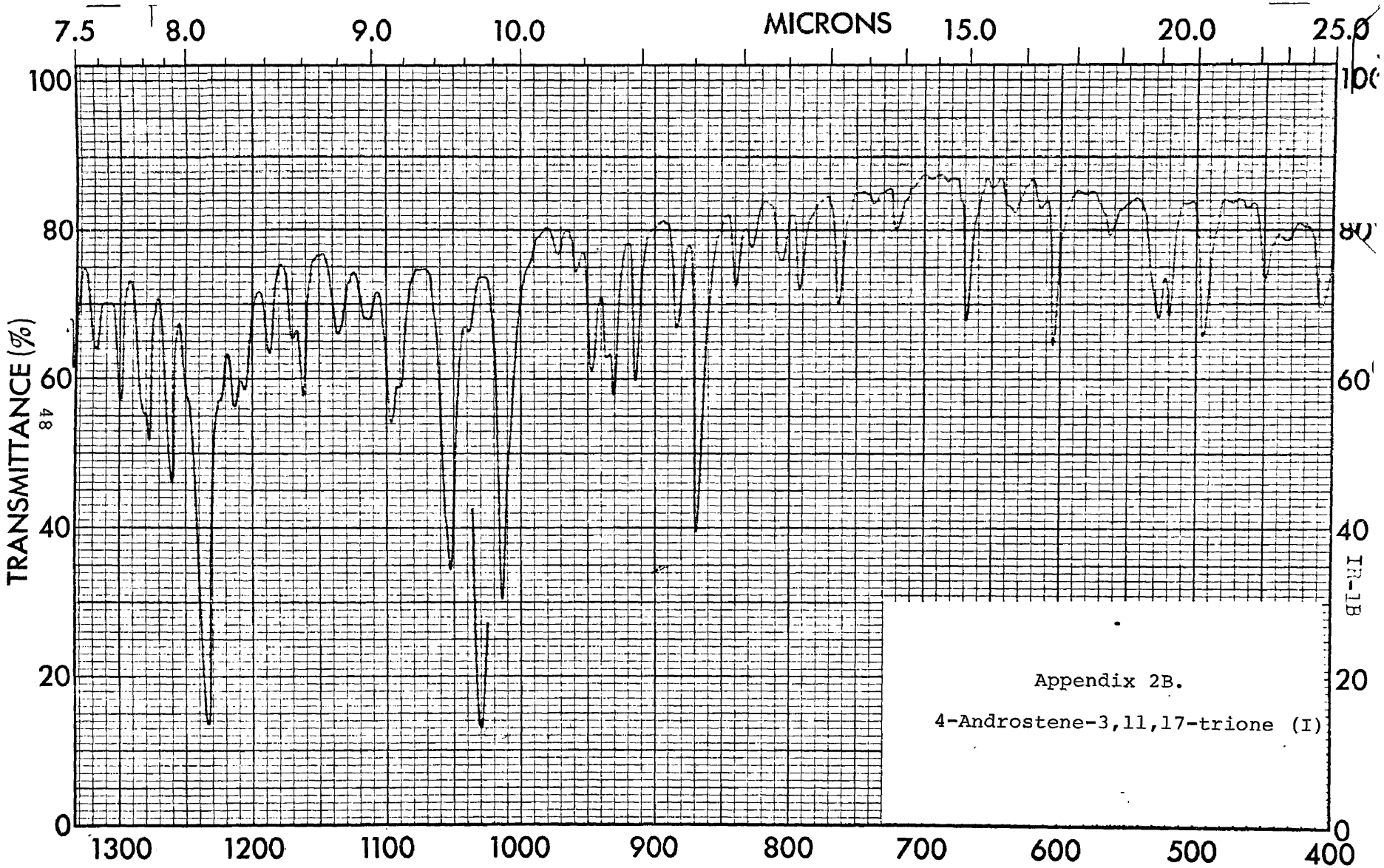


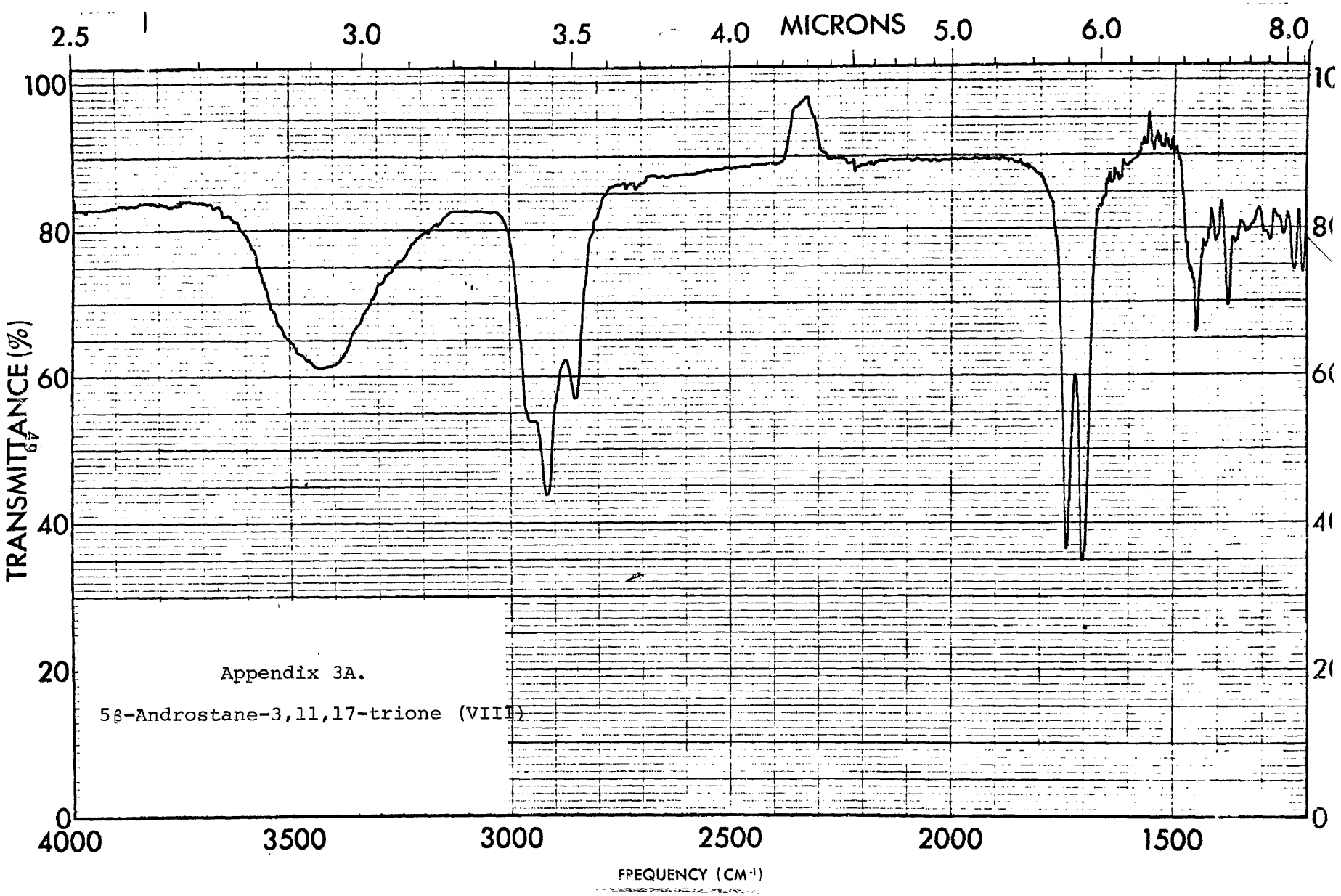
Appendix 1A.

4-Androstene-3,11,17-trione (I)



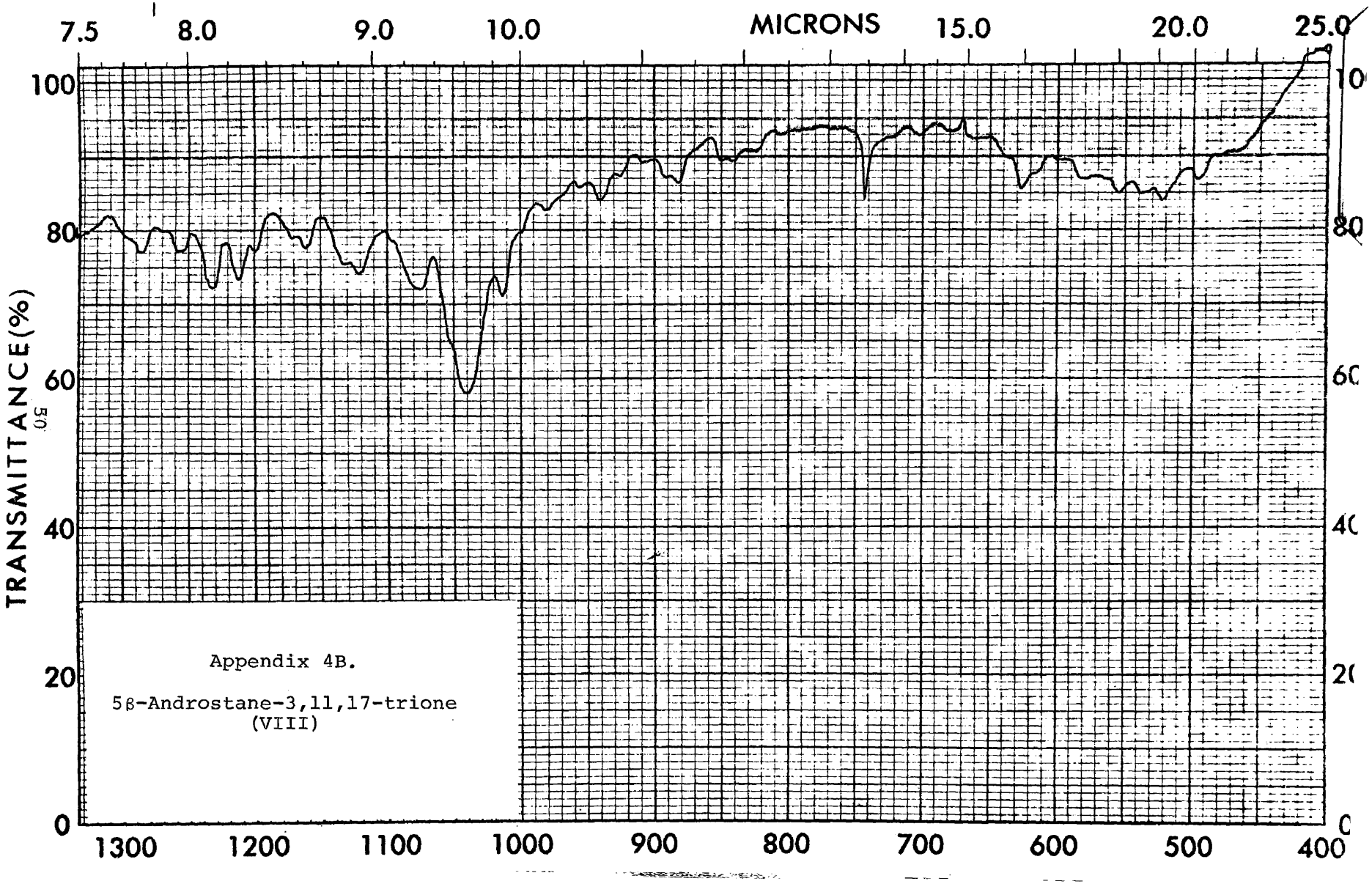
Appendix 2B.

4-Androstene-3,11,17-trione (I)



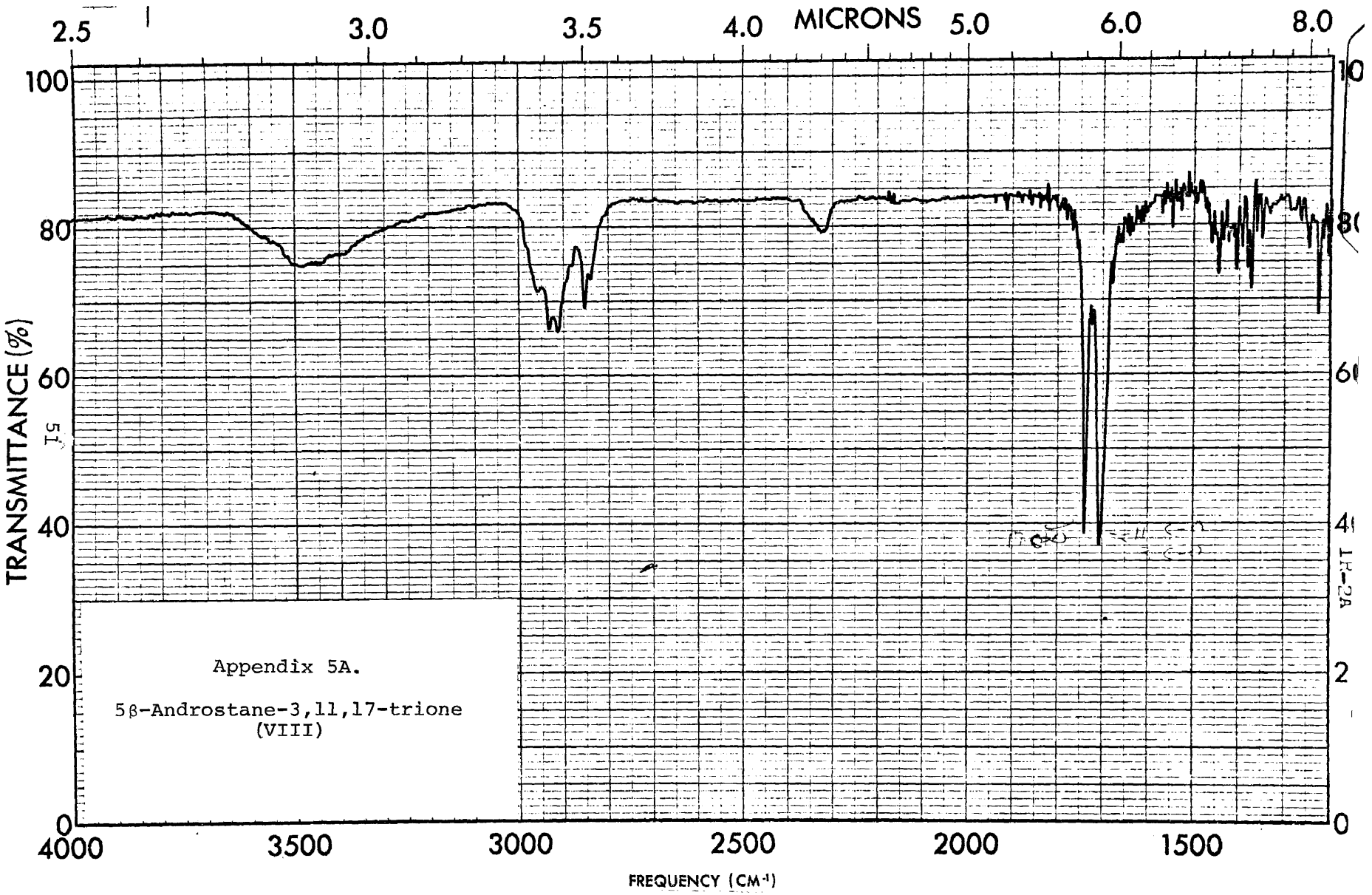
Appendix 3A.

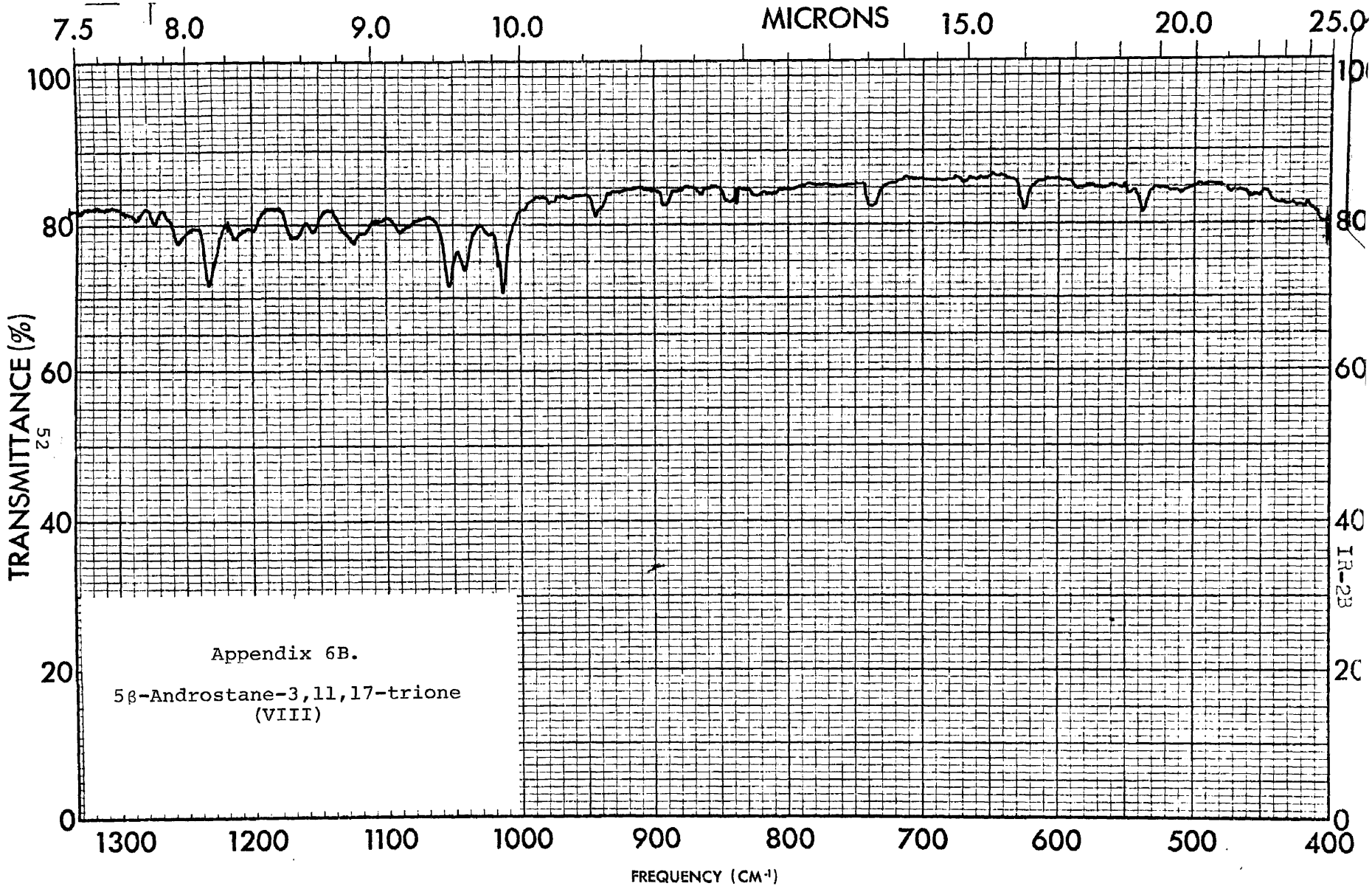
5β-Androstane-3,11,17-trione (VIII)

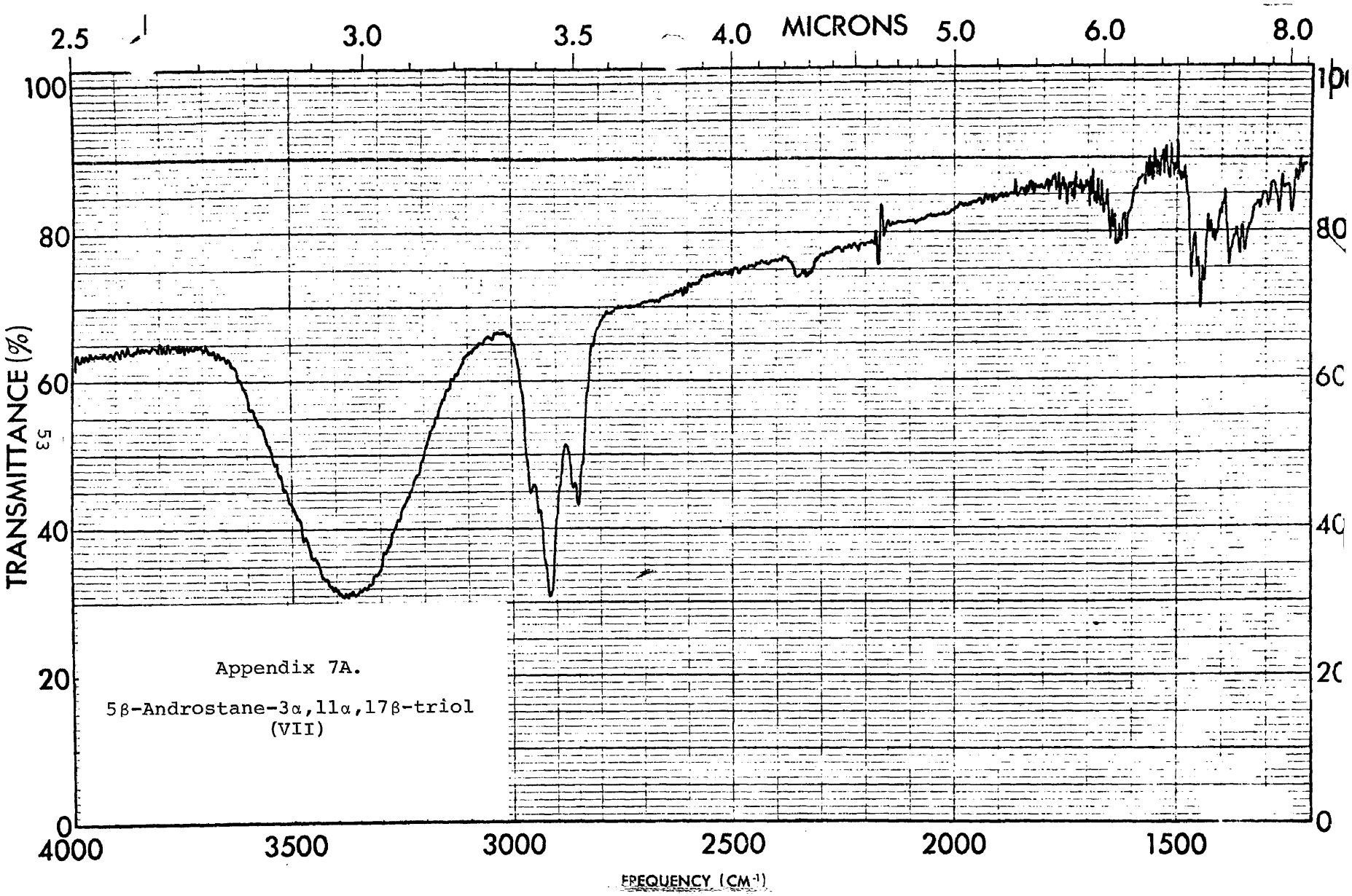


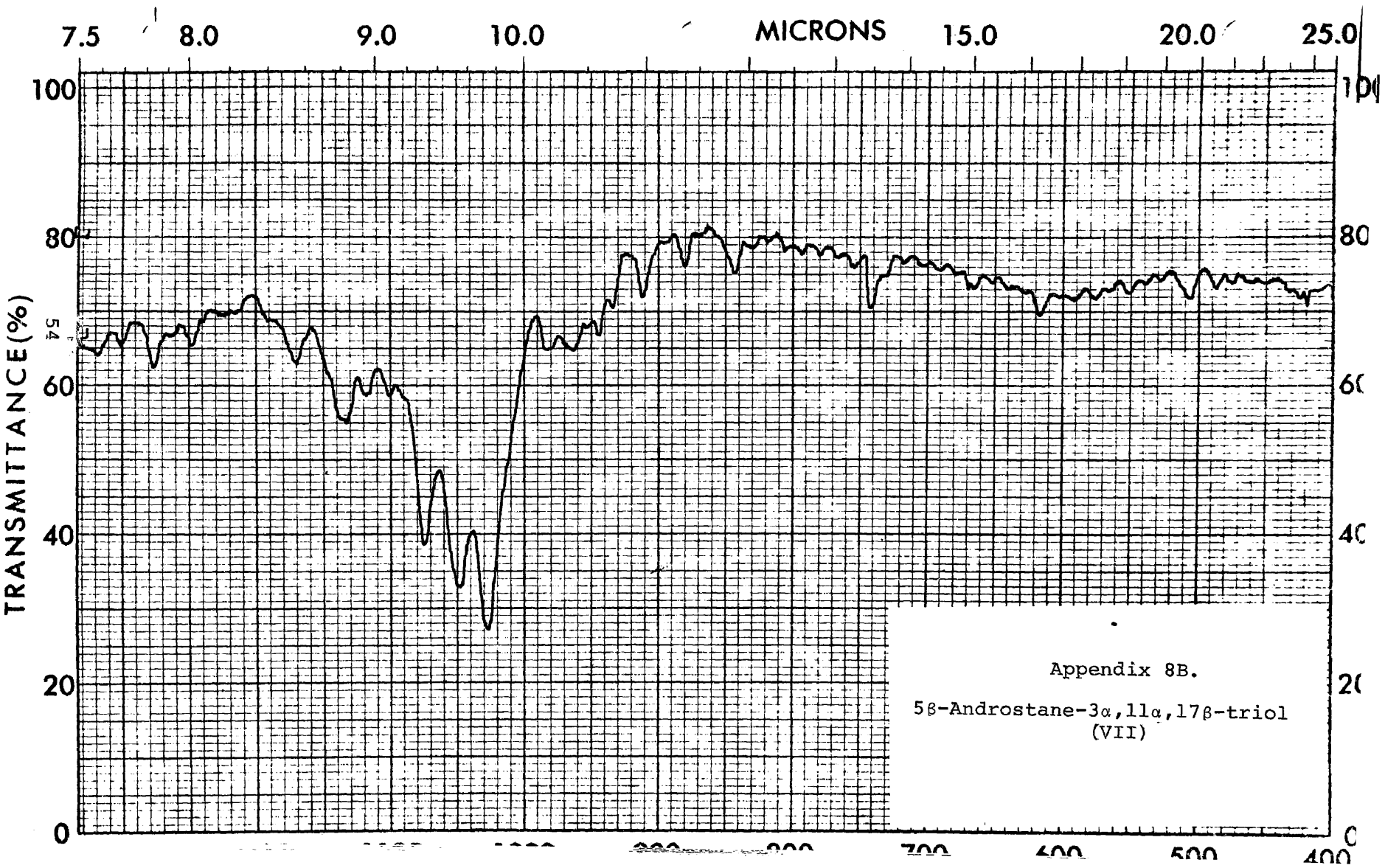
Appendix 4B.

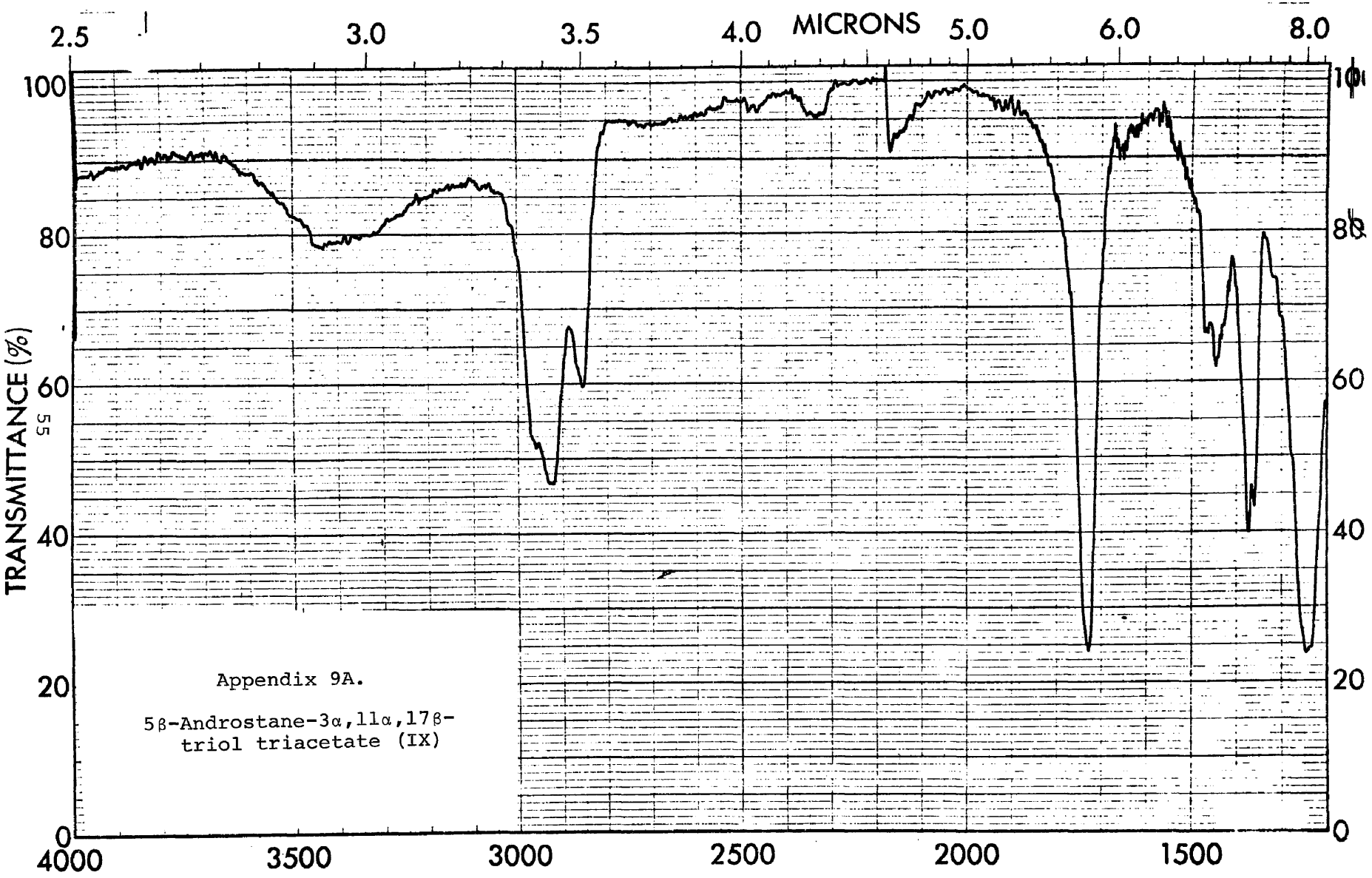
5β-Androstane-3,11,17-trione
(VIII)

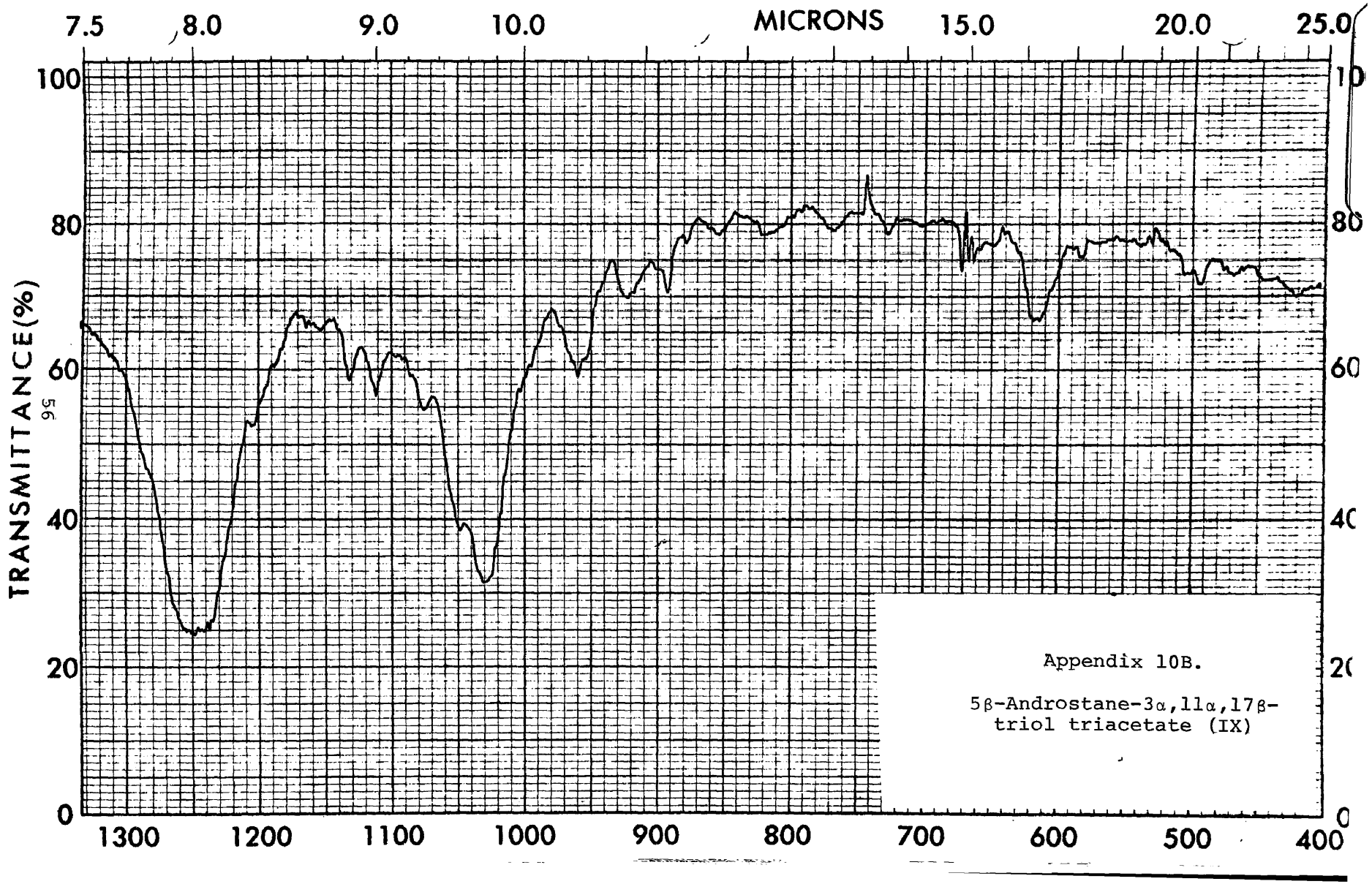

2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
100
80
60
40
20
0
TRANSMITTANCE (%)
4000
3500
3000
2500
2000
1500
FREQUENCY (CM-1)
Appendix 5A.
5β-Androstane-3,11,17-trione
(VIII)


7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
100
80
60
40
20
0
TRANSMITTANCE (%)
1300
1200
1100
1000
900
800
700
600
500
400
FREQUENCY (CM-1)
Appendix 6B.
5β-Androstane-3,11,17-trione
(VIII)
52
IR-23


2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
100
80
60
40
20
0
TRANSMITTANCE (%)
53
4000
3500
3000
2500
2000
1500
FREQUENCY (CM-1)
Appendix 7A.
5β-Androstane-3α,11α,17β-triol
(VII)

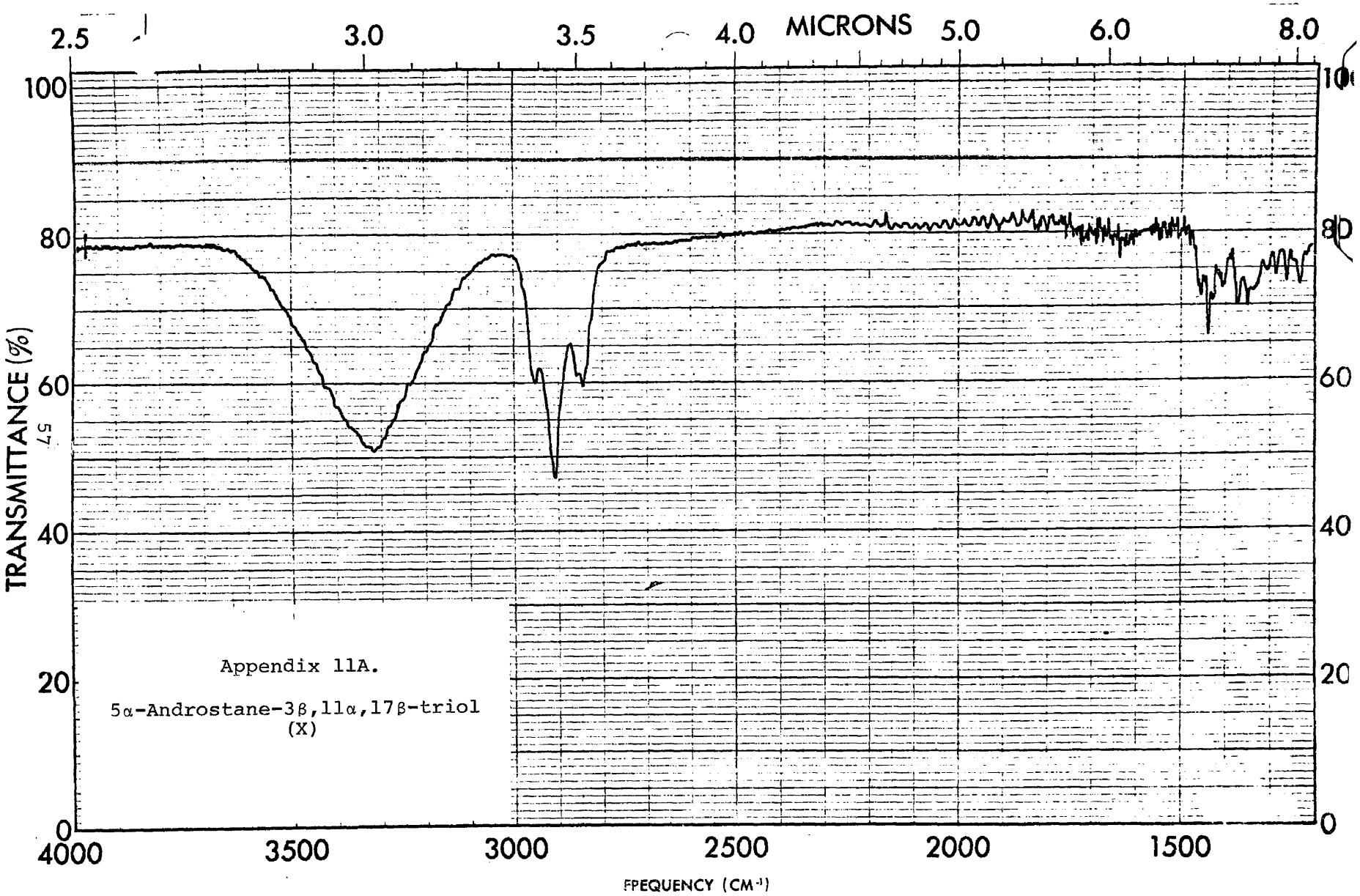

7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
100
80
60
40
20
0
TRANSMITTANCE(%)
54
Appendix 8B.
5β-Androstane-3α,11α,17β-triol
(VII)

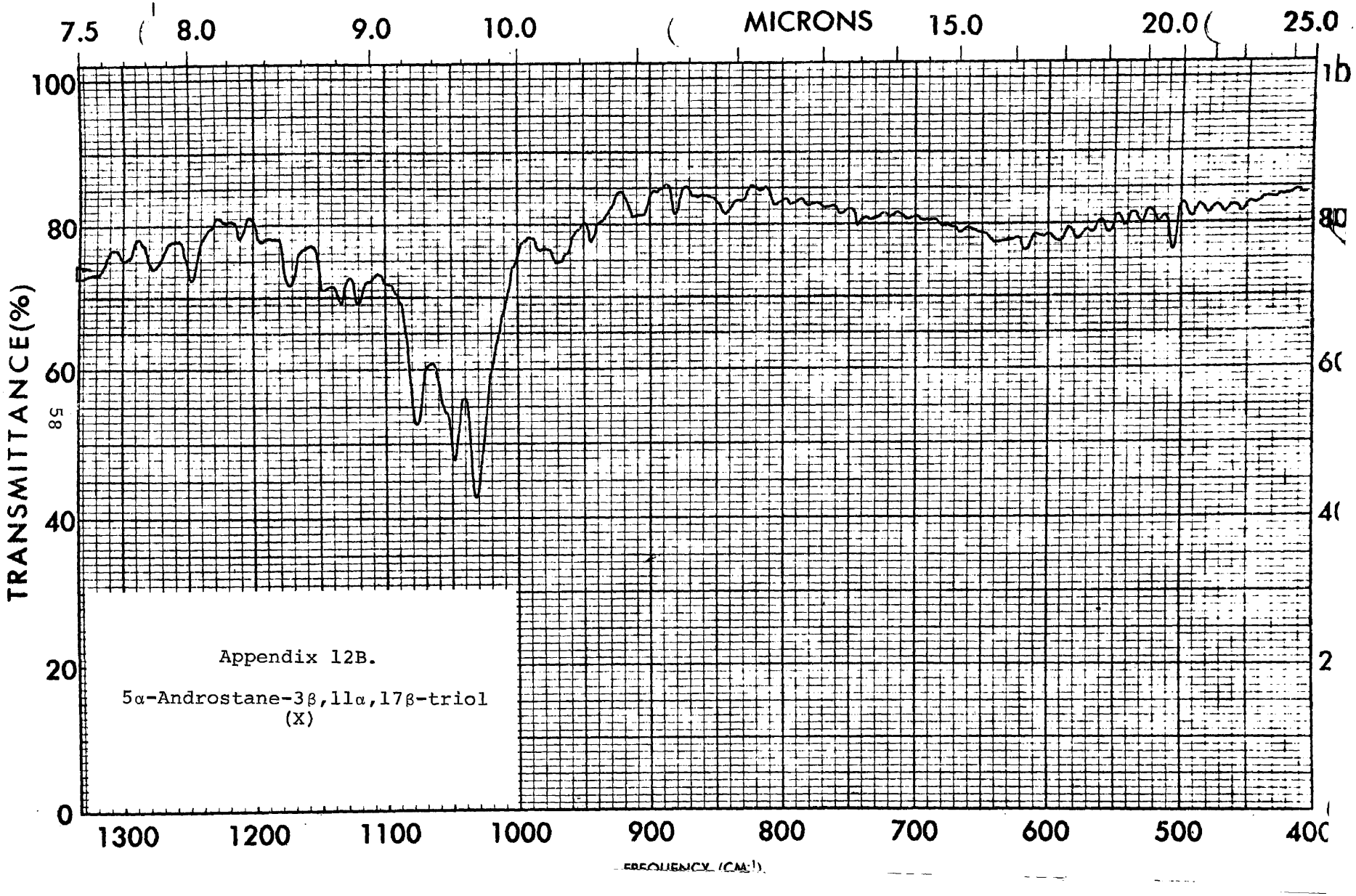

2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
100
80
60
40
20
0
TRANSMITTANCE (%)
55
4000
3500
3000
2500
2000
1500
Appendix 9A.
5β-Androstane-3α,11α,17β-triol triacetate (IX)



Appendix 10B.

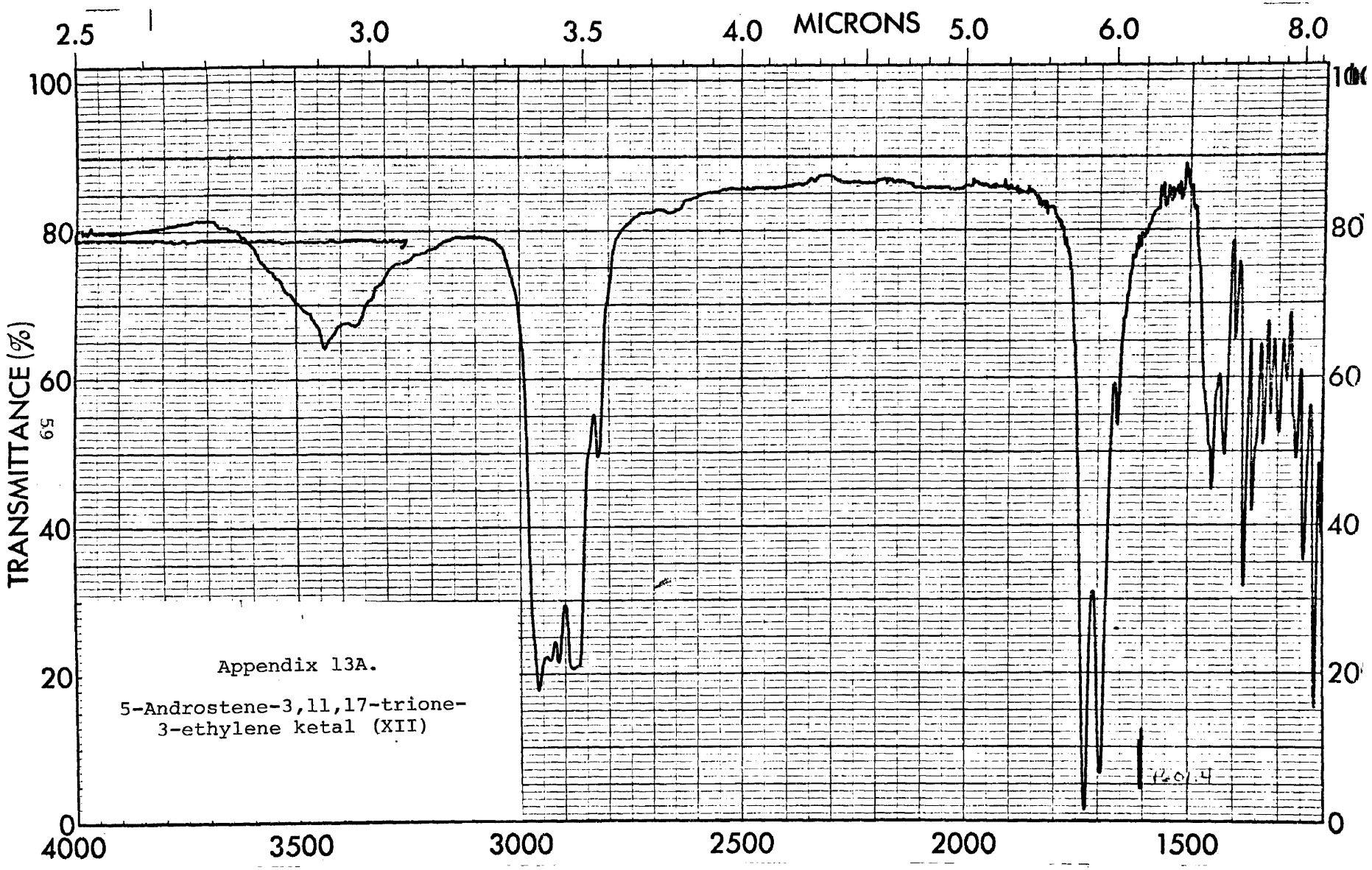
5β-Androstane-3α,11α,17β-triol triacetate (IX)

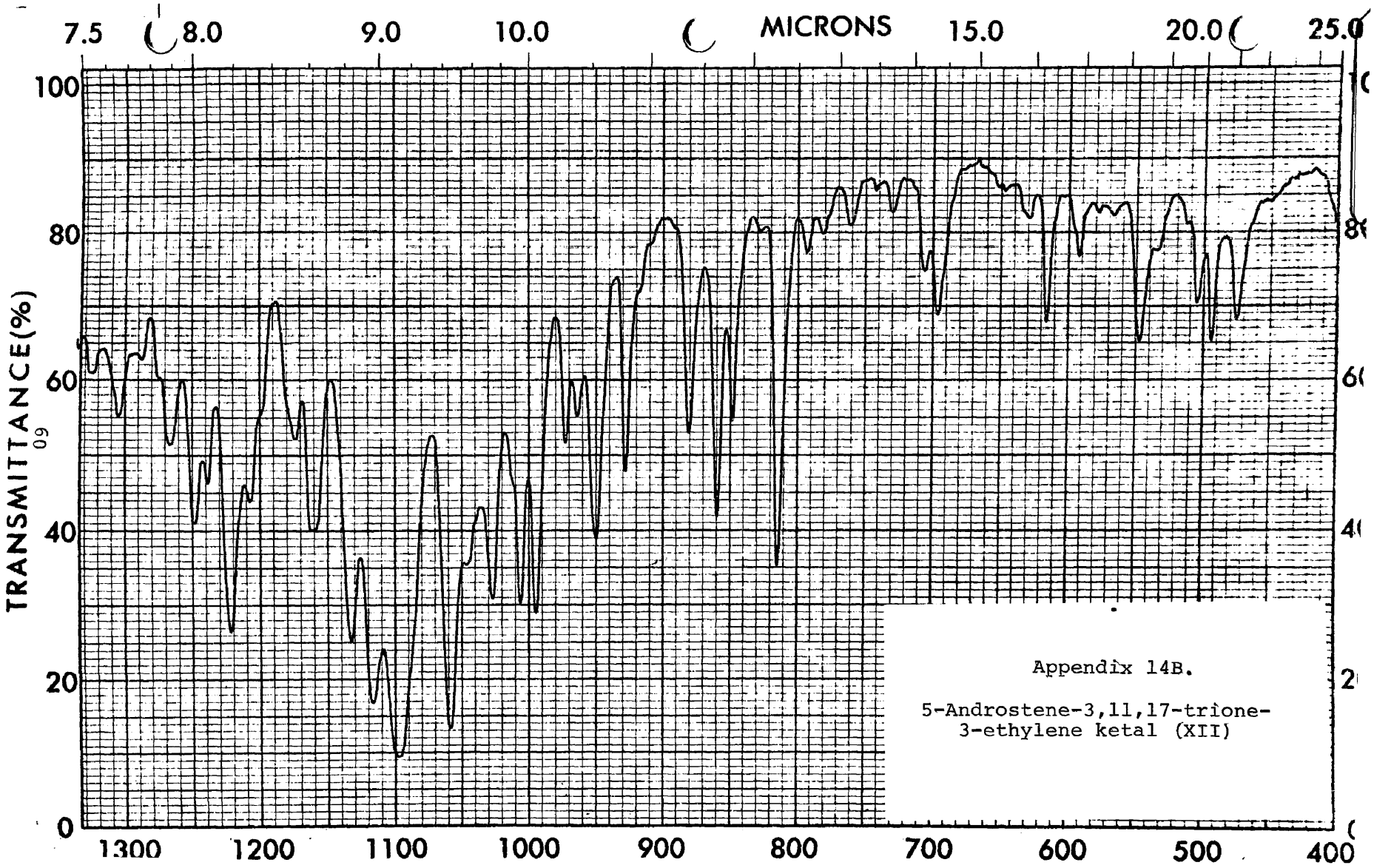

2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
100
80
60
40
20
0
TRANSMITTANCE (%)
4000
3500
3000
2500
2000
1500
FREQUENCY (CM⁻¹)
Appendix 11A.
5α-Androstane-3β,11α,17β-triol
(X)



Appendix 12B.

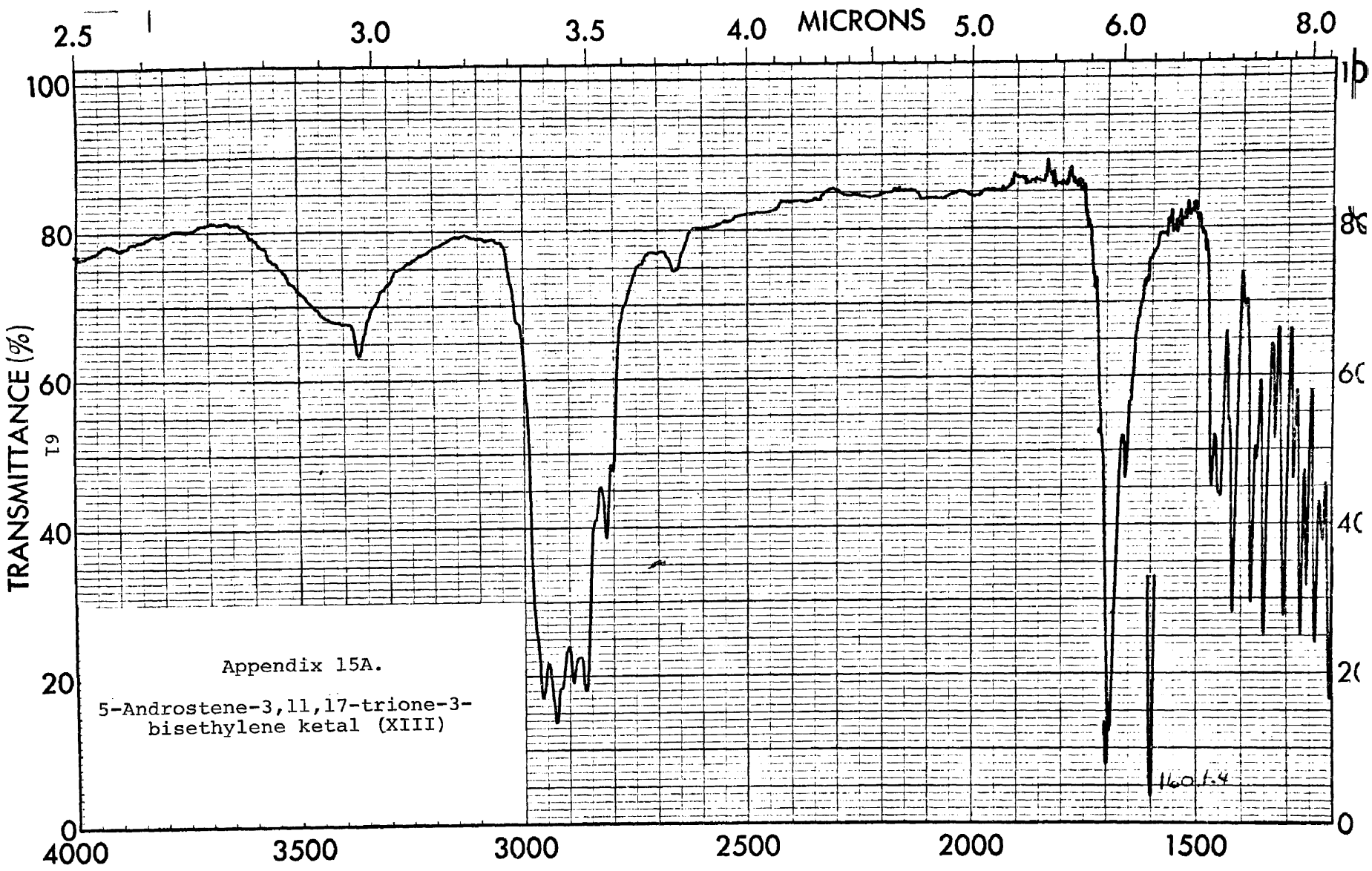
5α-Androstane-3β,11α,17β-triol
(X)


2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
100
80
60
40
20
0
TRANSMITTANCE (%)
4000
3500
3000
2500
2000
1500
Appendix 13A.
5-Androstene-3,11,17-trione-
3-ethylene ketal (XII)



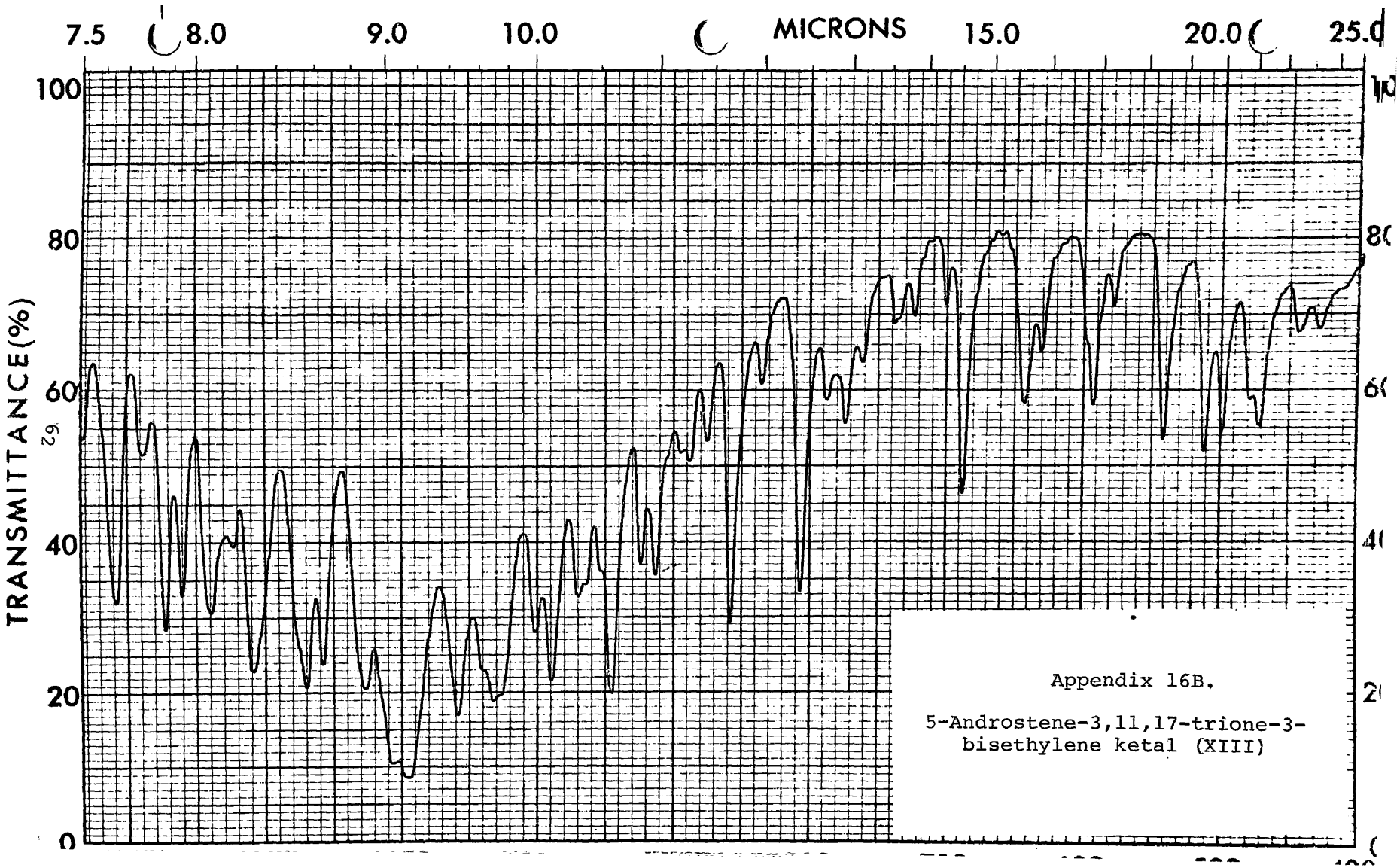
Appendix 14B.

5-Androstene-3,11,17-trione-
3-ethylene ketal (XII)



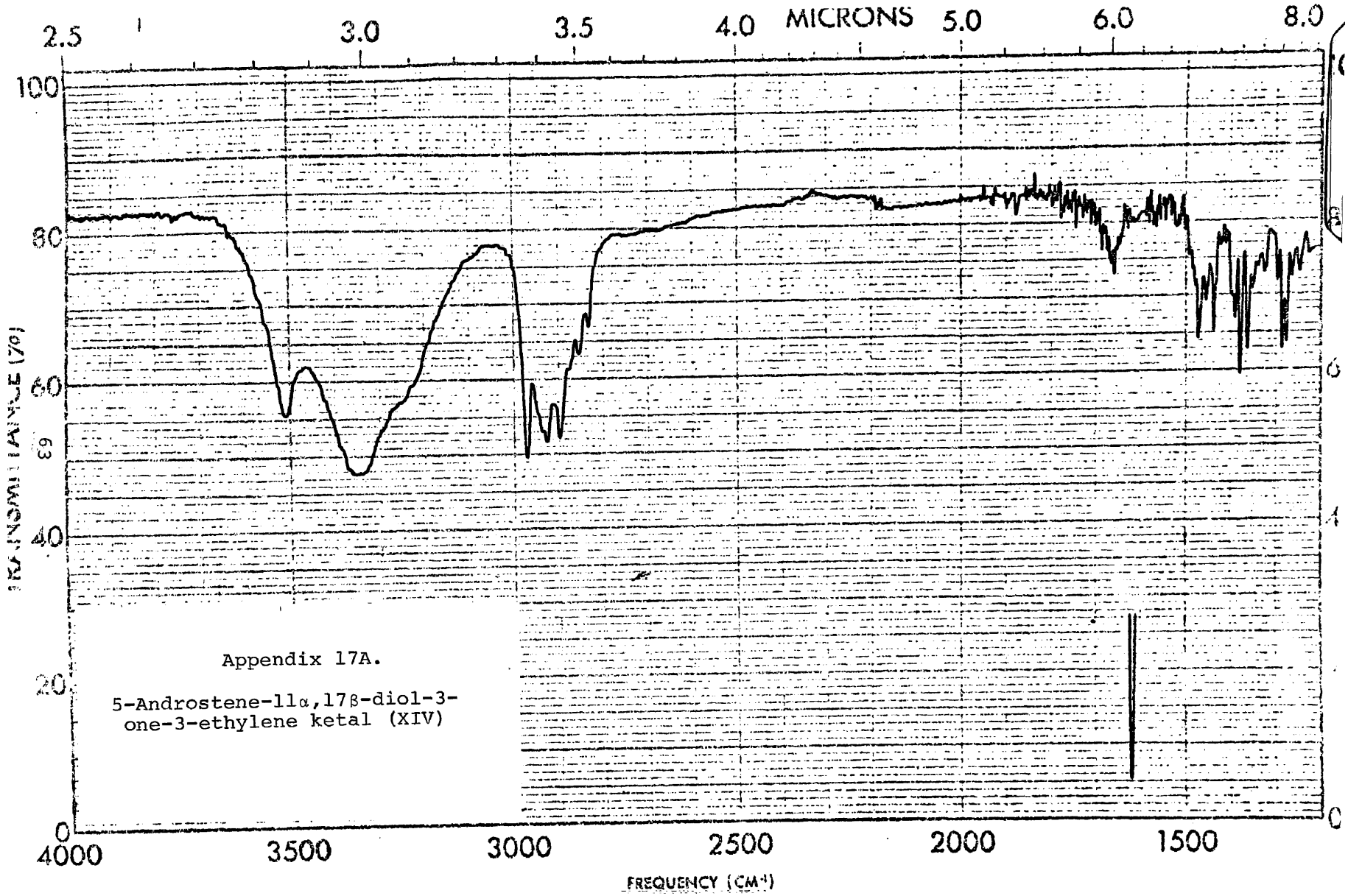
Appendix 15A.

5-Androstene-3,11,17-trione-3-bisethylene ketal (XIII)



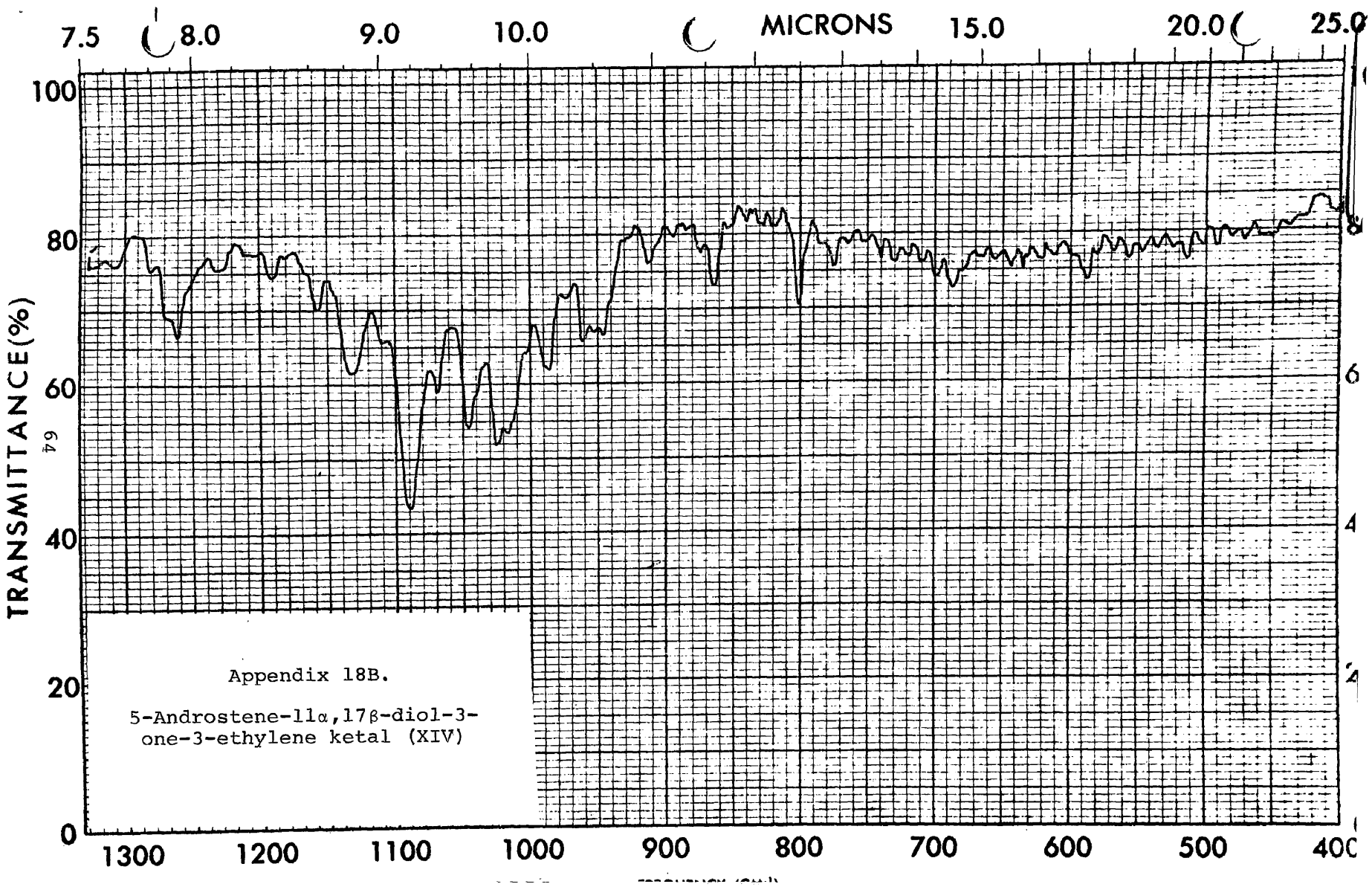
Appendix 16B.

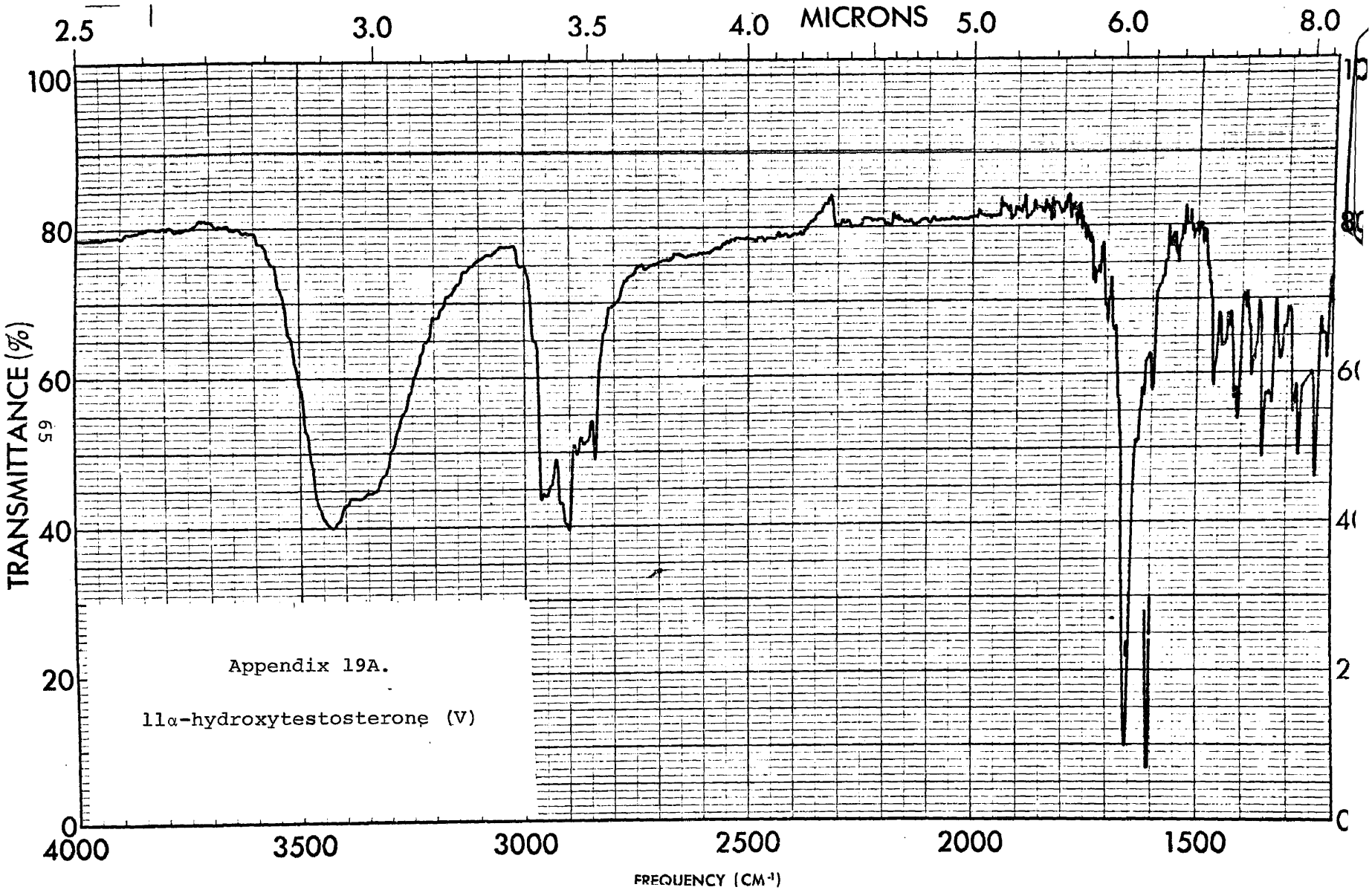
5-Androstene-3,11,17-trione-3-bisethylene ketal (XIII)



Appendix 17A.

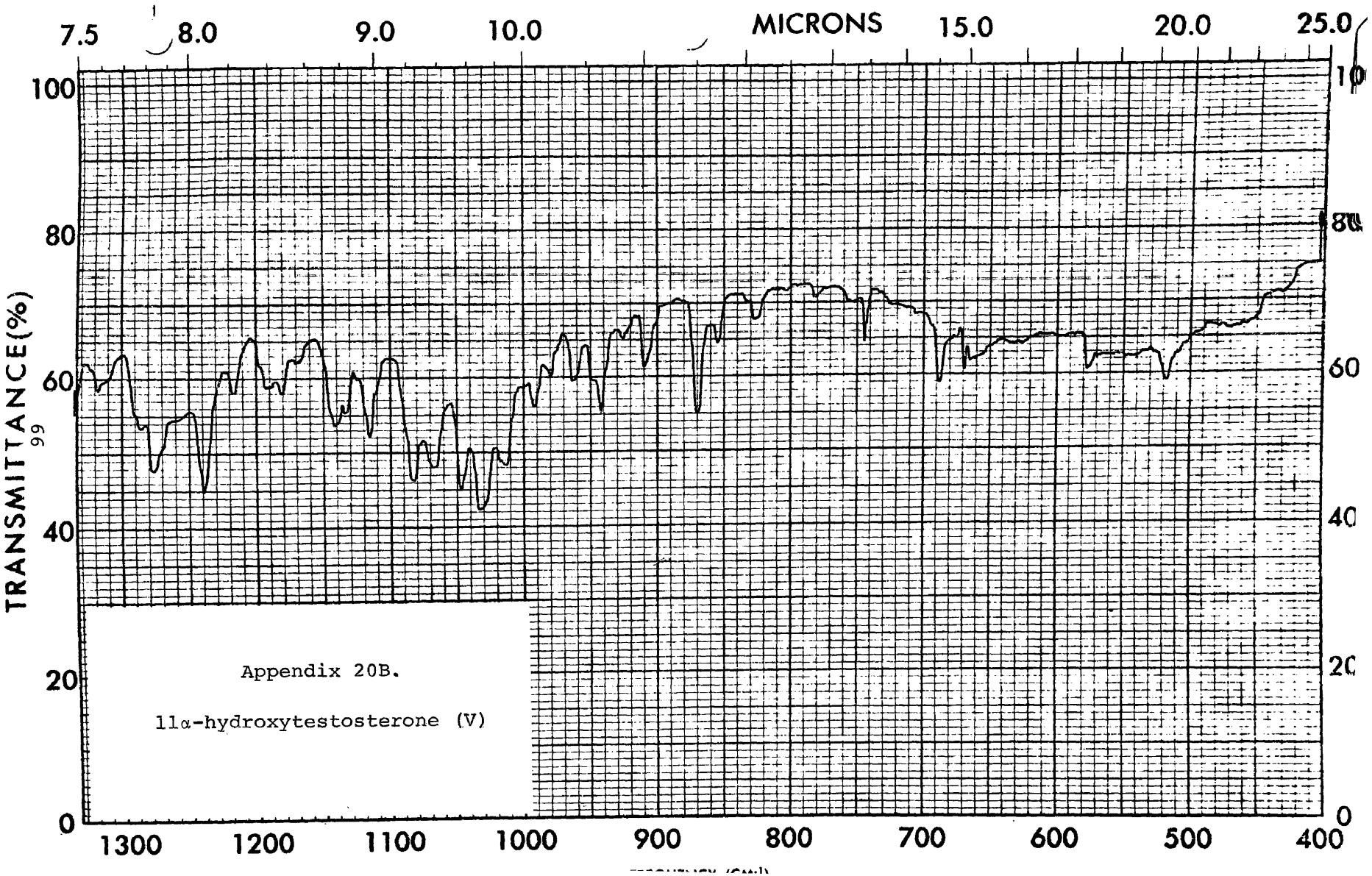
5-Androstene-11α,17β-diol-3-one-3-ethylene ketal (XIV)

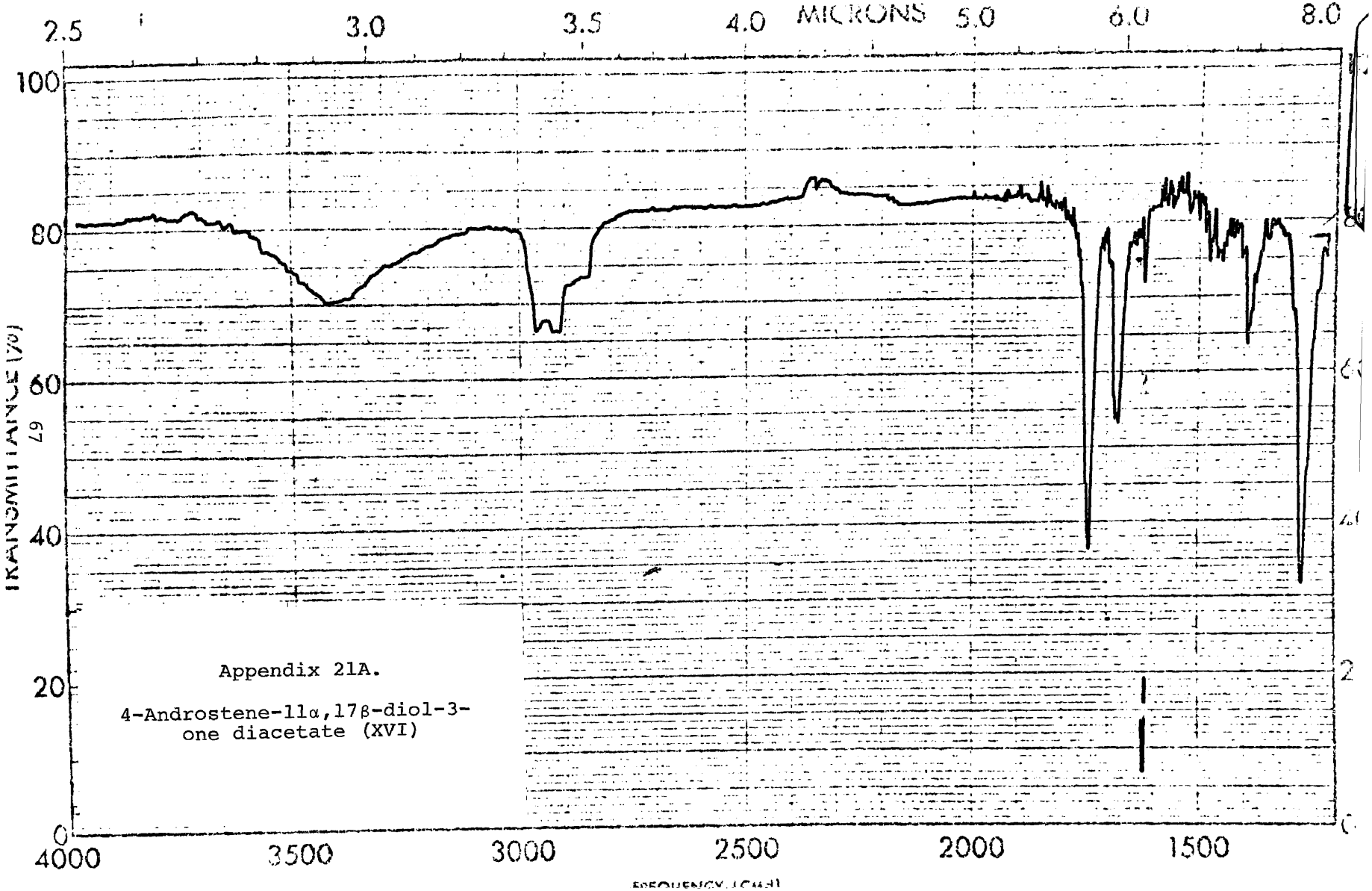

7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
100
80
60
40
20
0
TRANSMITTANCE(%)
1300
1200
1100
1000
900
800
700
600
500
400
Appendix 18B.
5-Androstene-11α,17β-diol-3-one-3-ethylene ketal (XIV)



Appendix 19A.

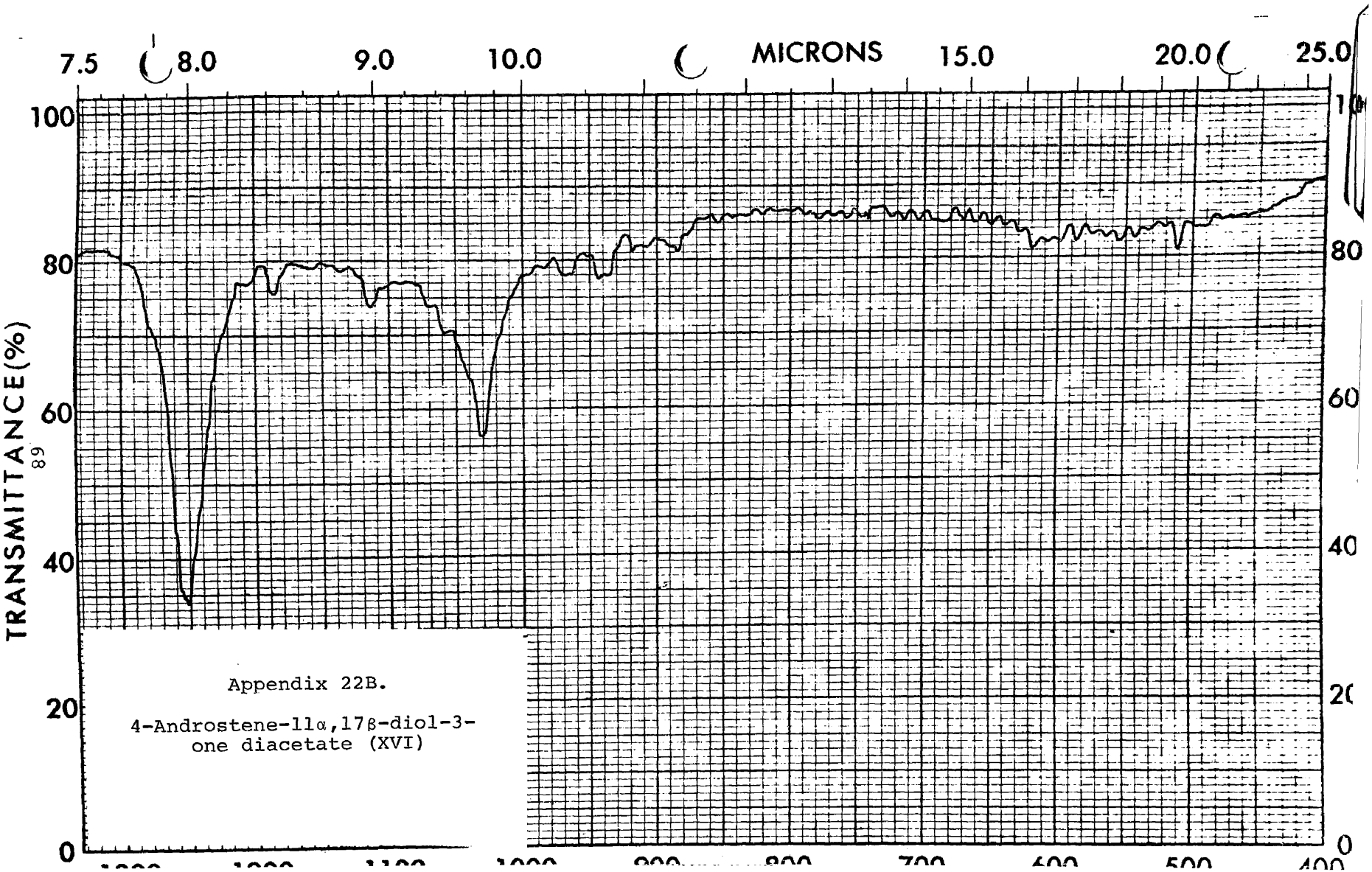
11α-hydroxytestosterone (V)


7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
100
80
60
40
20
0
TRANSMITTANCE(%)
1300
1200
1100
1000
900
800
700
600
500
400
Appendix 20B.
11α-hydroxytestosterone (V)



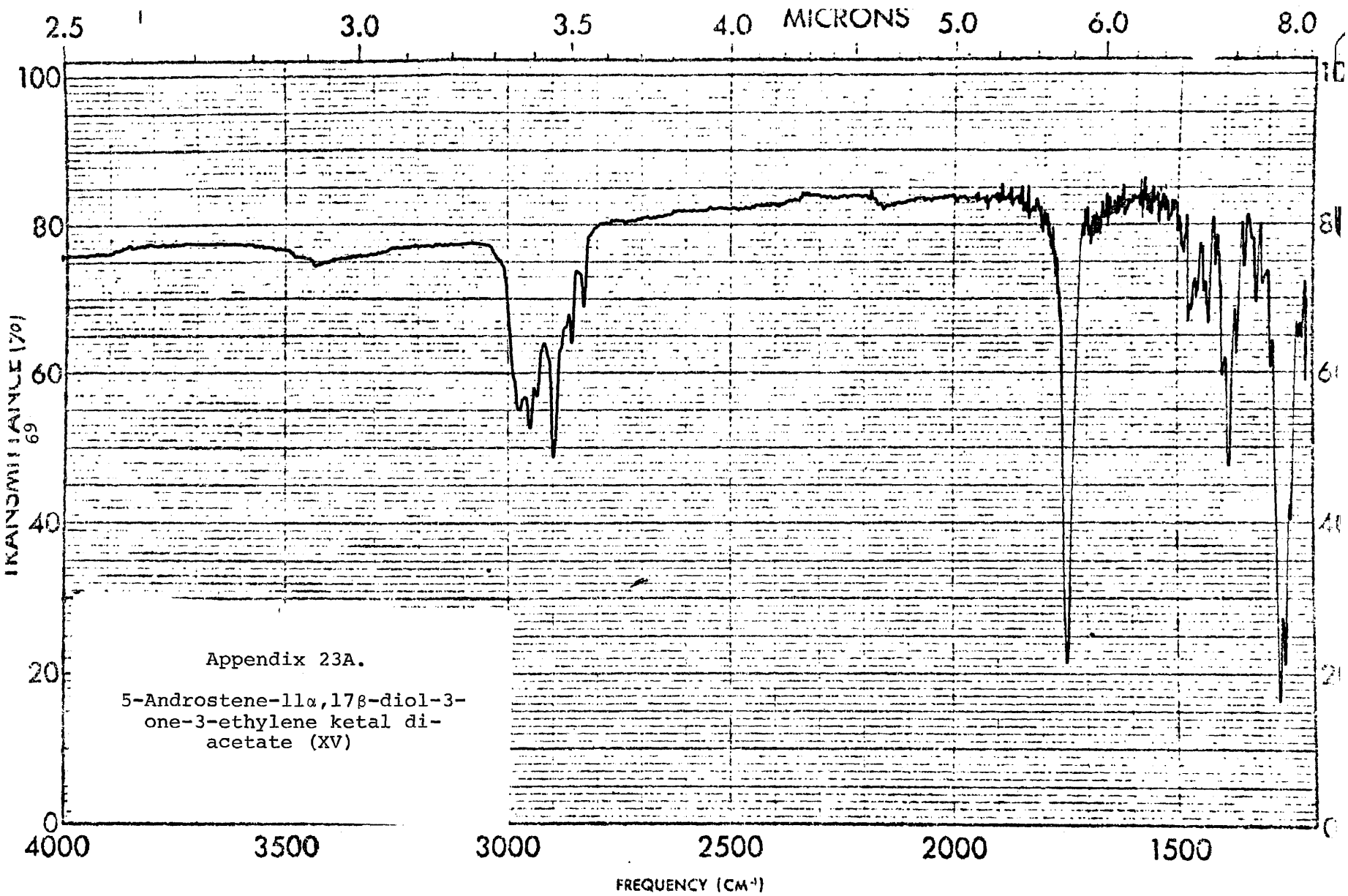
Appendix 21A.

4-Androstene-11α,17β-diol-3-one diacetate (XVI)



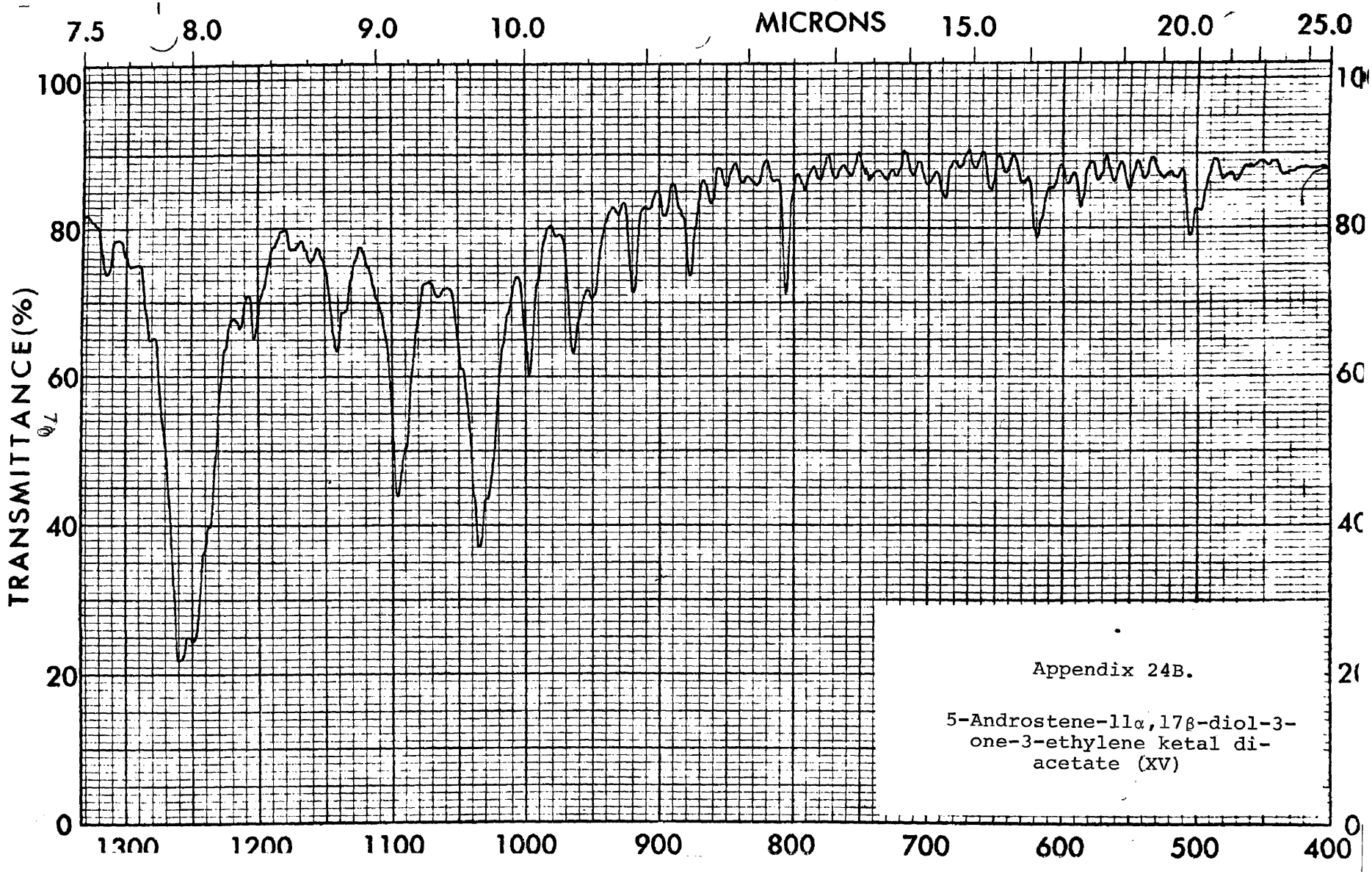
Appendix 22B.

4-Androstene-11α,17β-diol-3-one diacetate (XVI)



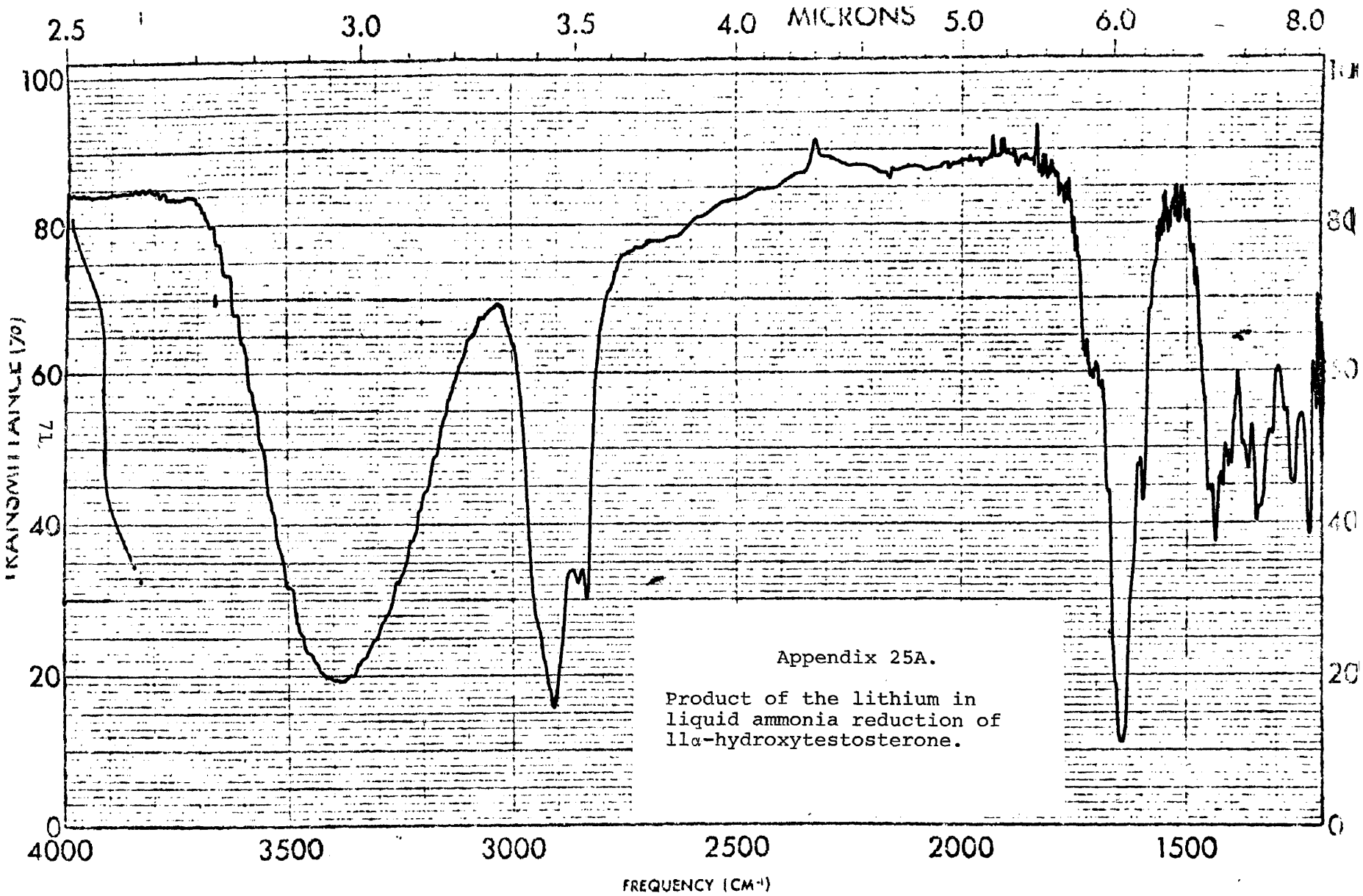
Appendix 23A.

5-Androstene-11α,17β-diol-3-one-3-ethylene ketal di-acetate (XV)



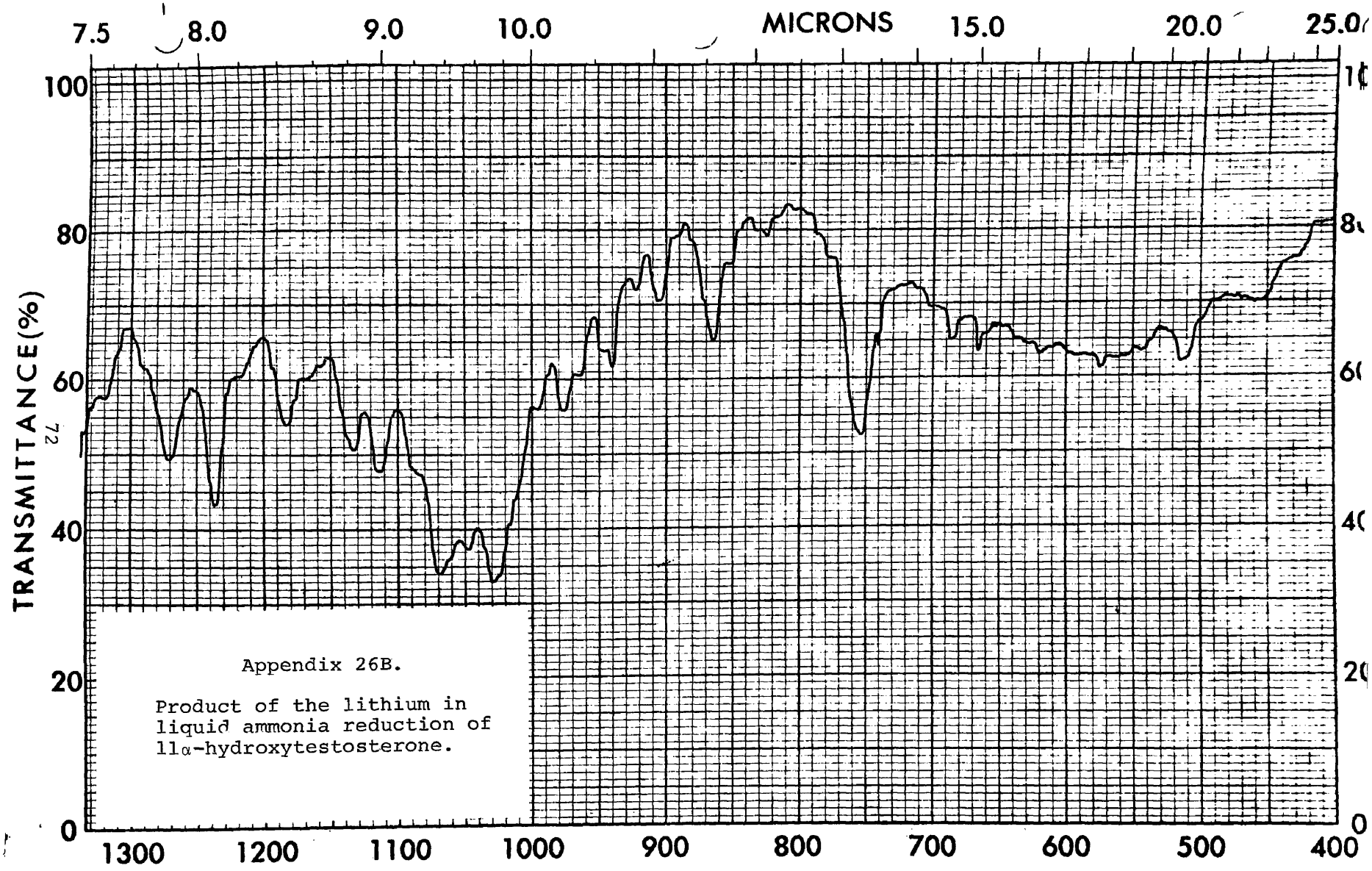
Appendix 24B.

5-Androstene-11α,17β-diol-3-one-3-ethylene ketal diacetate (XV)



Appendix 25A.

Product of the lithium in liquid ammonia reduction of 11α-hydroxytestosterone.

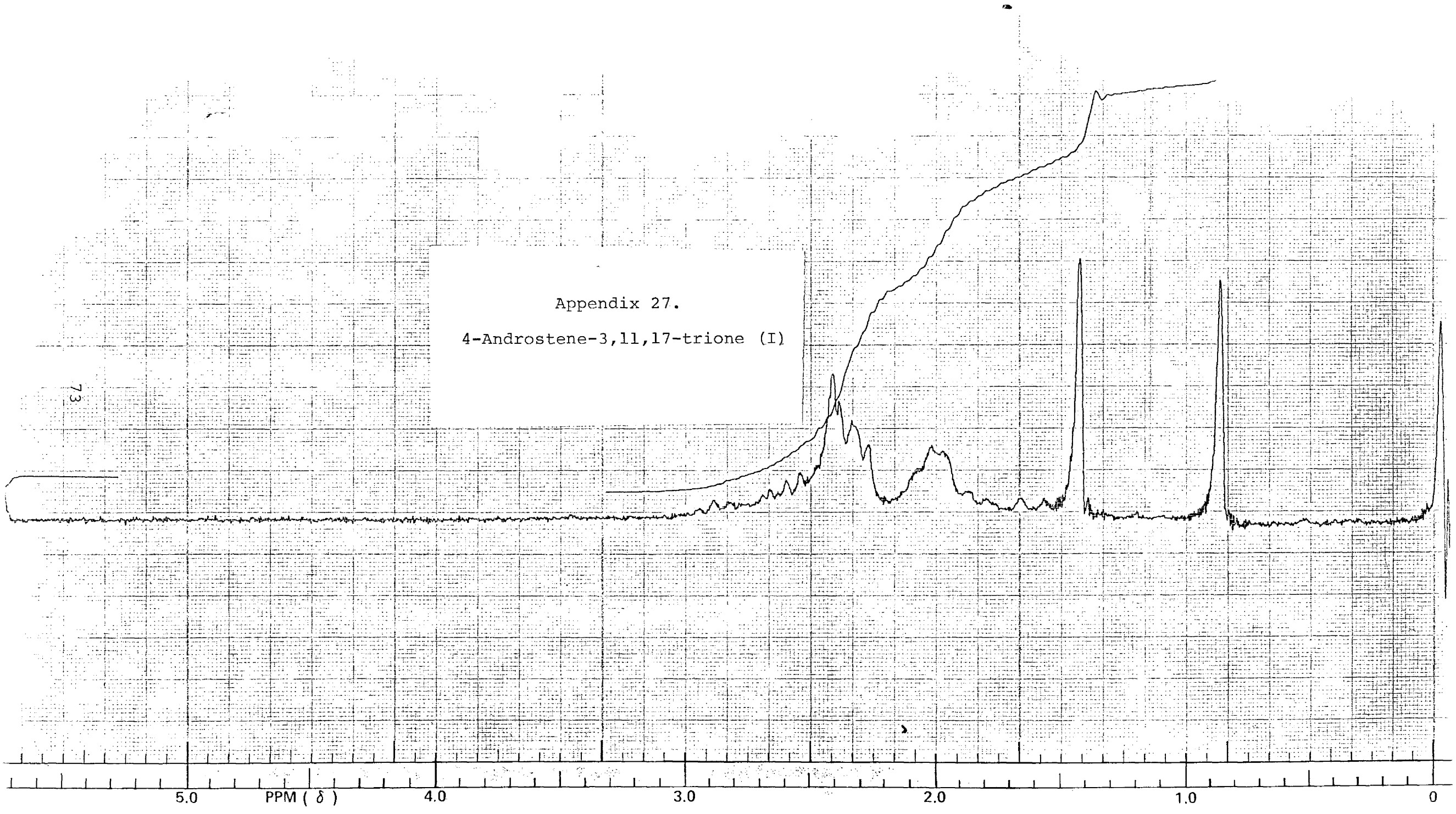


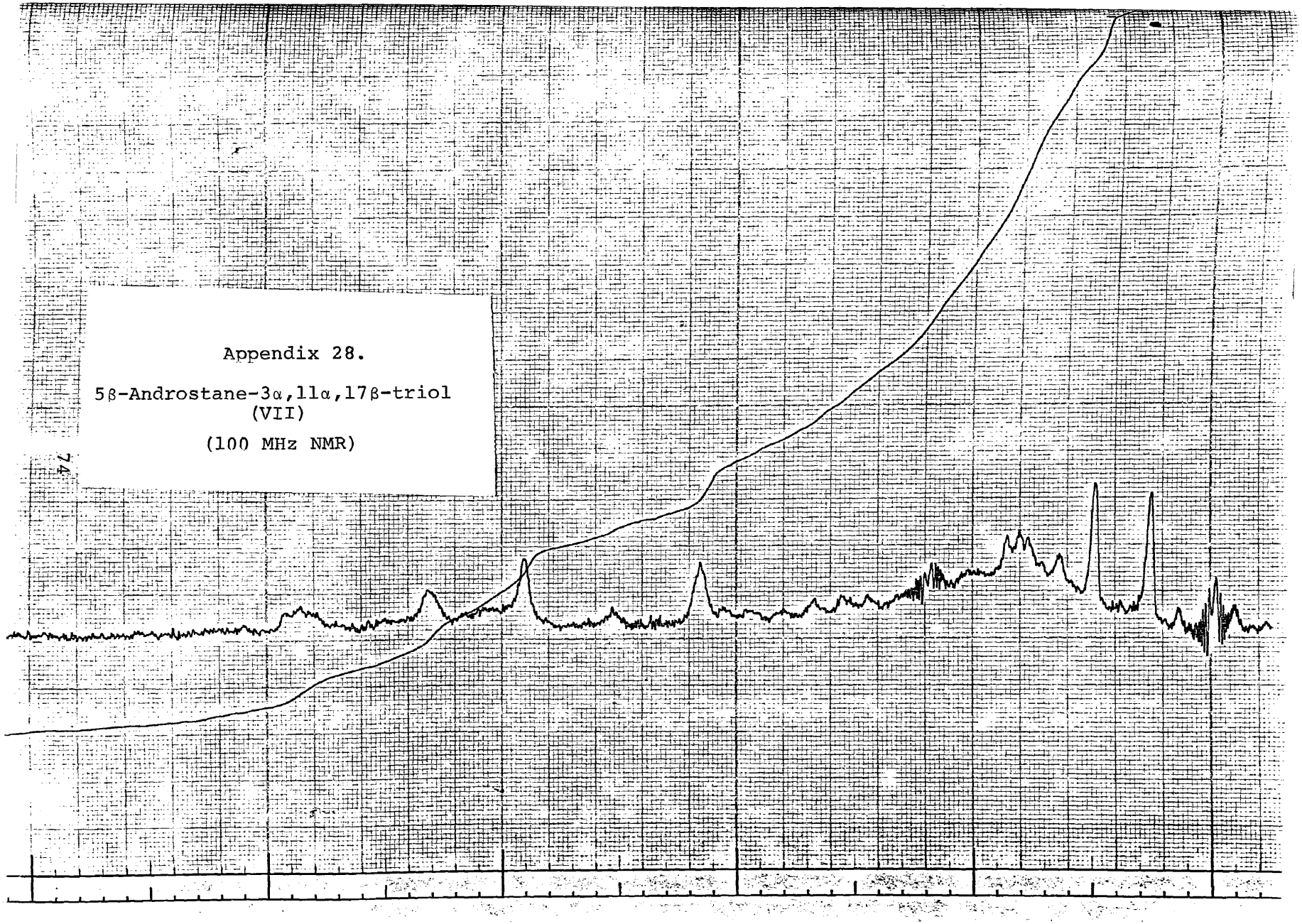
Appendix 26B.

Product of the lithium in liquid ammonia reduction of 11α-hydroxytestosterone.

Appendix 27.

4-Androstene-3,11,17-trione (I)





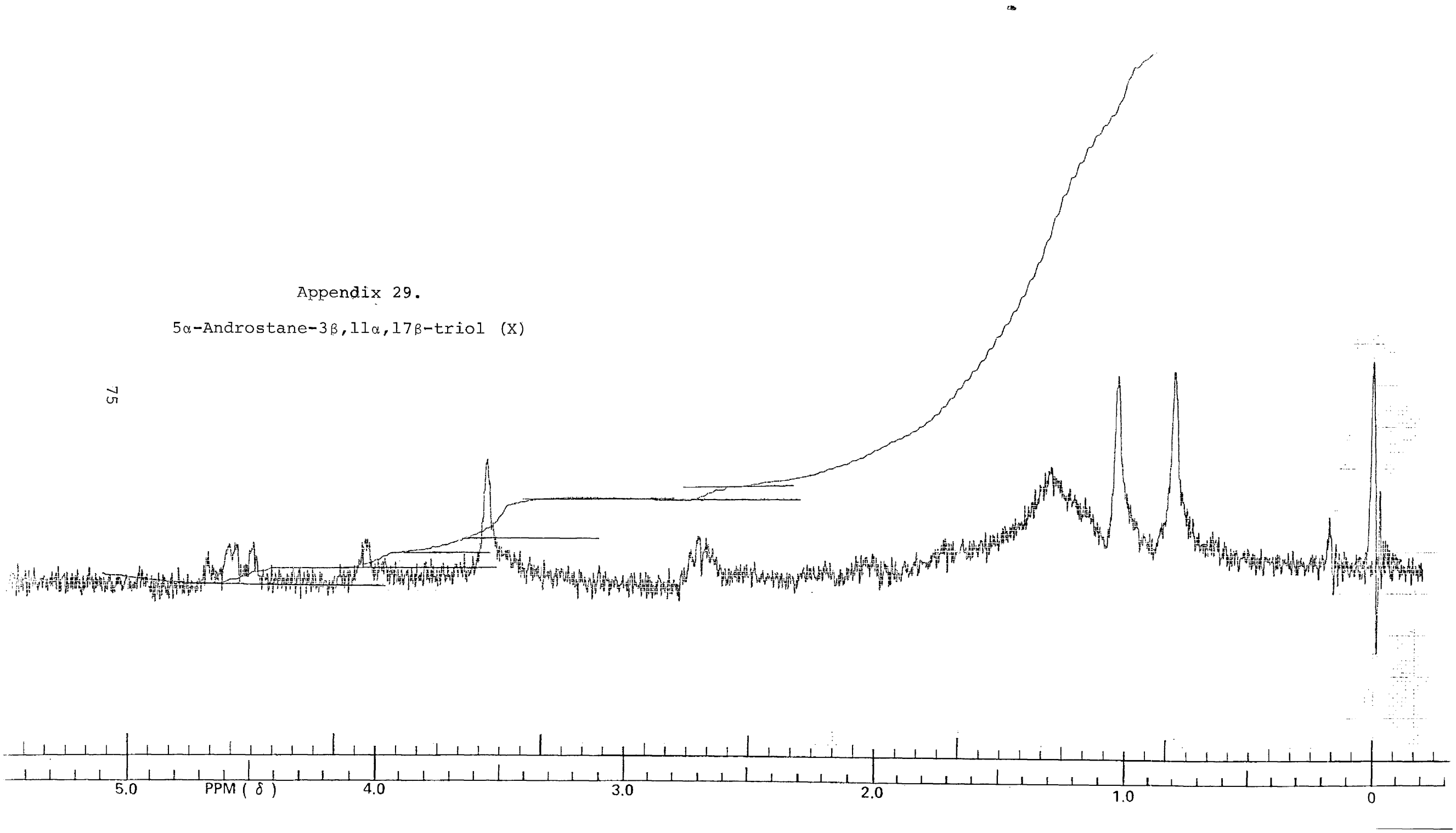
Appendix 28.

5β-Androstane-3α,11α,17β-triol
(VII)

(100 MHz NMR)

Appendix 29.

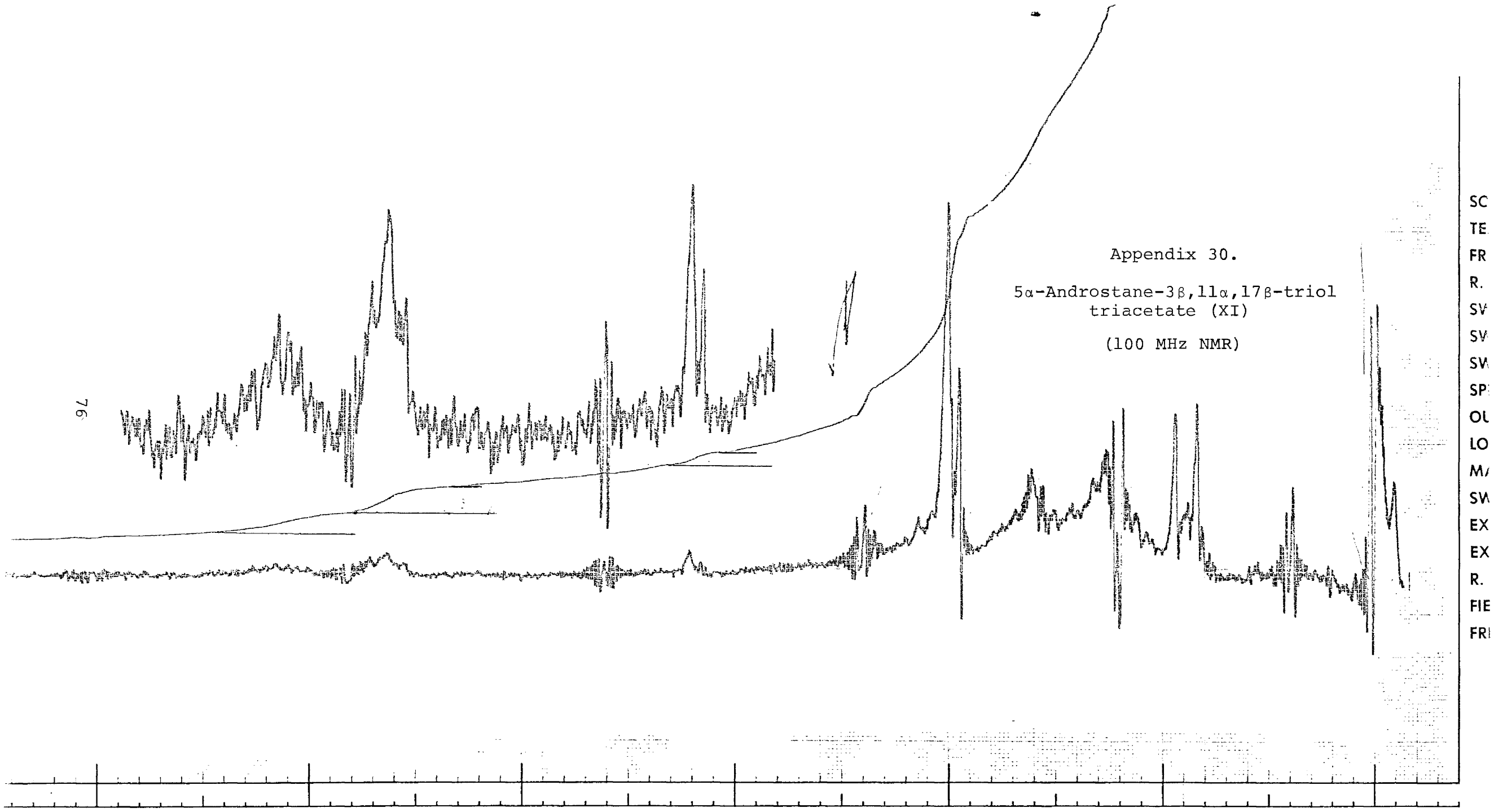
5α-Androstane-3β,11α,17β-triol (X)

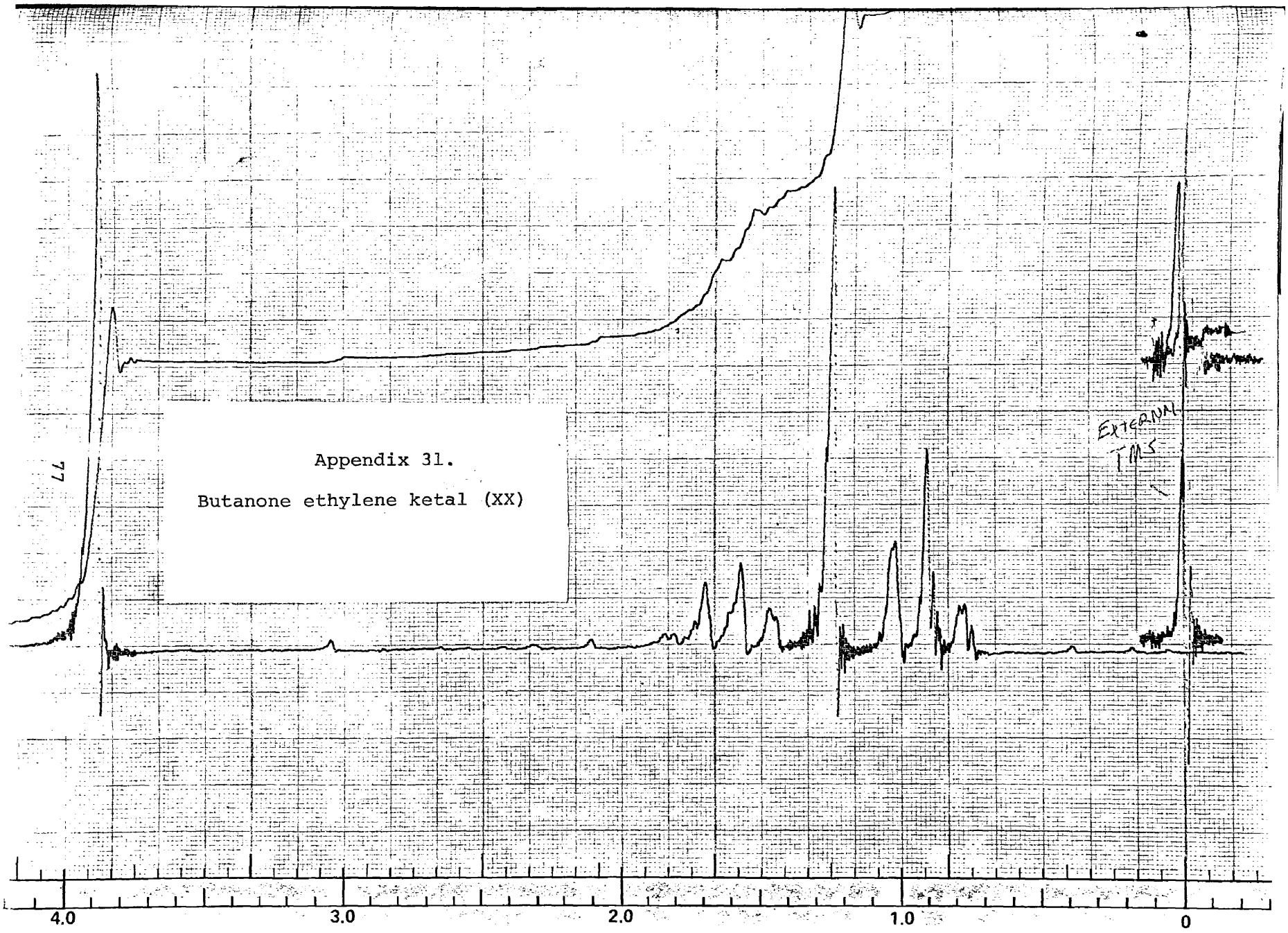


Appendix 30.

5α-Androstane-3β,11α,17β-triol triacetate (XI)

(100 MHz NMR)





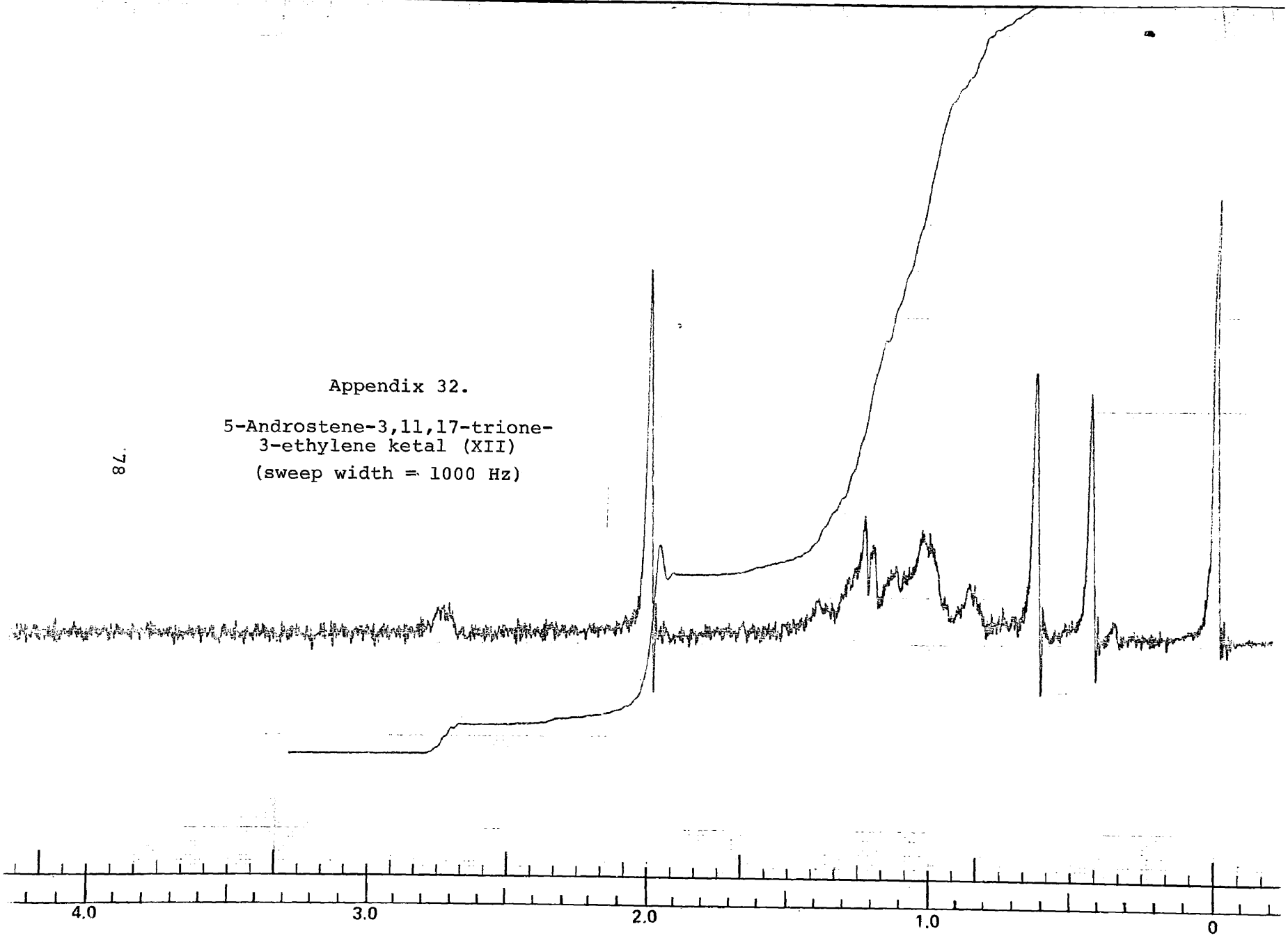
Appendix 31.

Butanone ethylene ketal (XX)

Appendix 32.

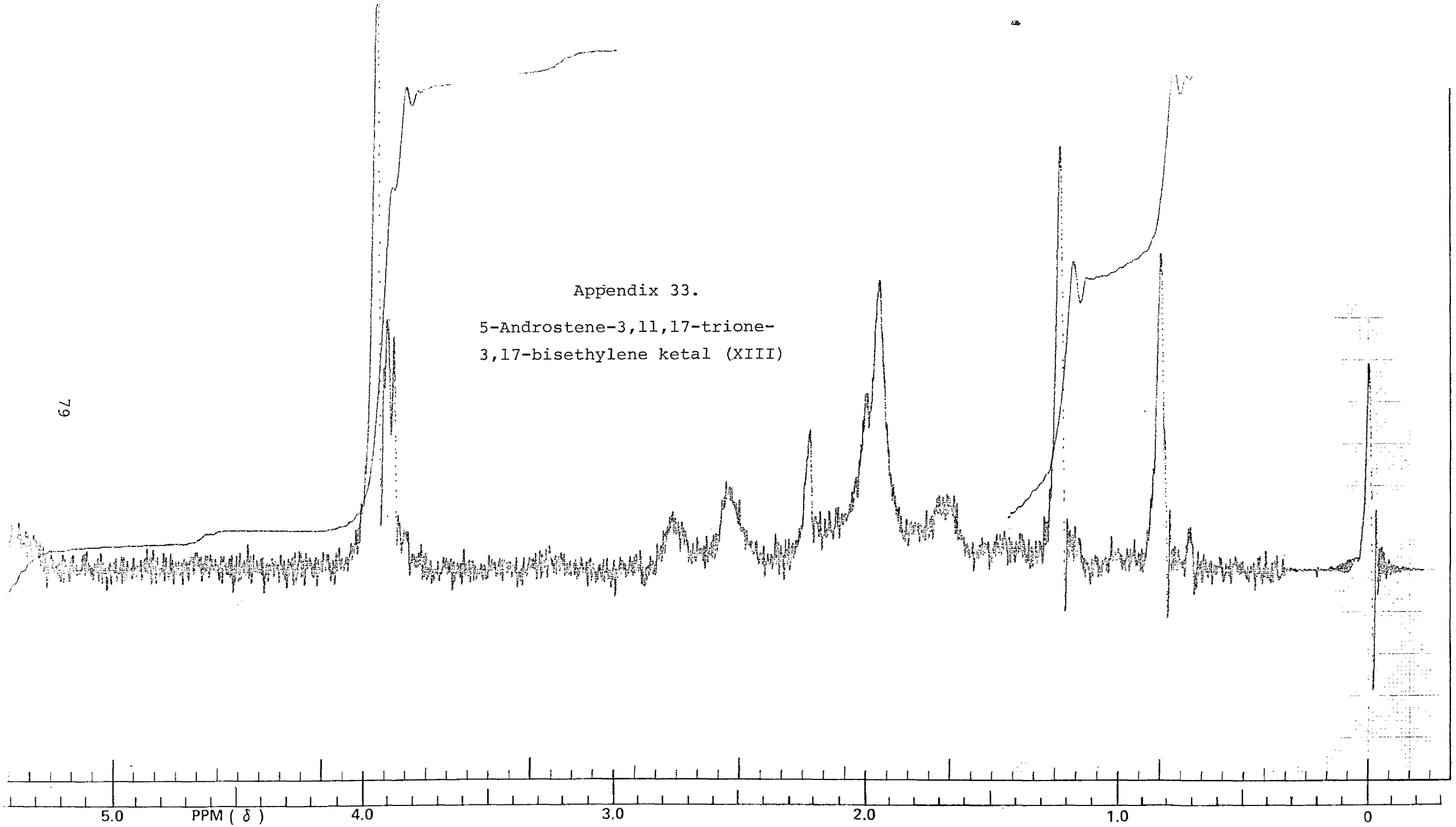
5-Androstene-3,11,17-trione-
3-ethylene ketal (XII)

(sweep width = 1000 Hz)



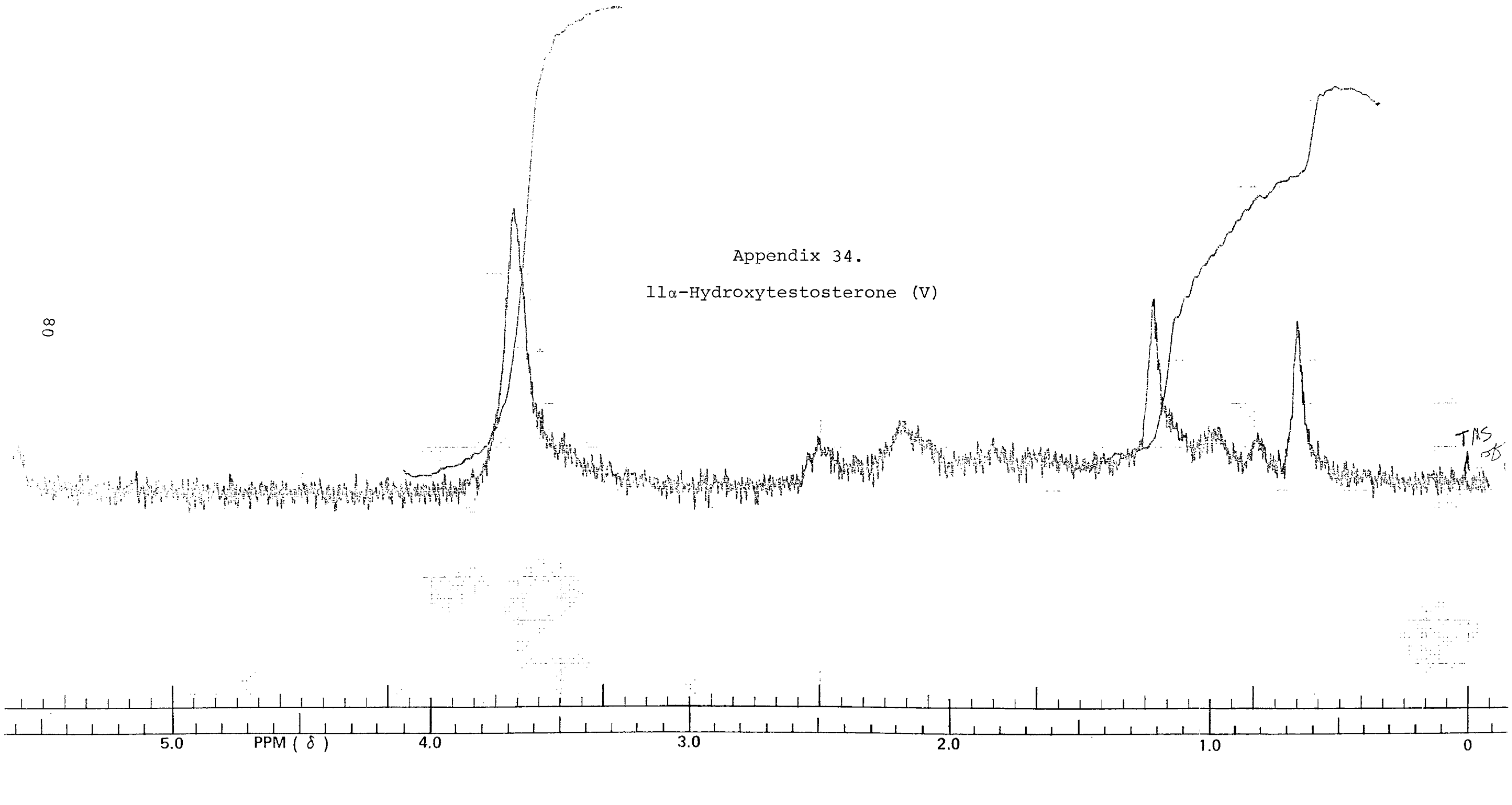
Appendix 33.

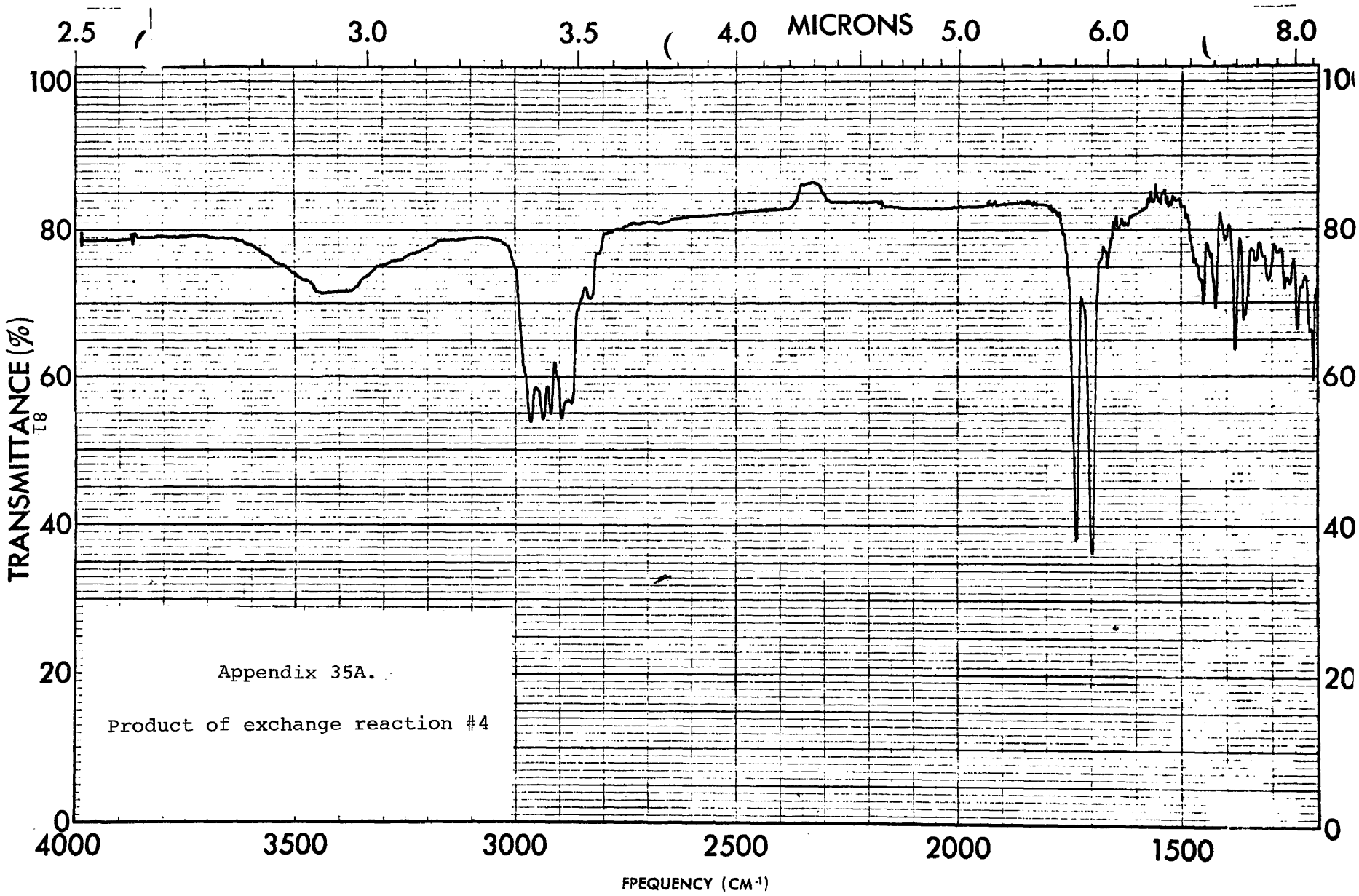
5-Androstene-3,11,17-trione-
3,17-bisethylene ketal (XIII)



Appendix 34.

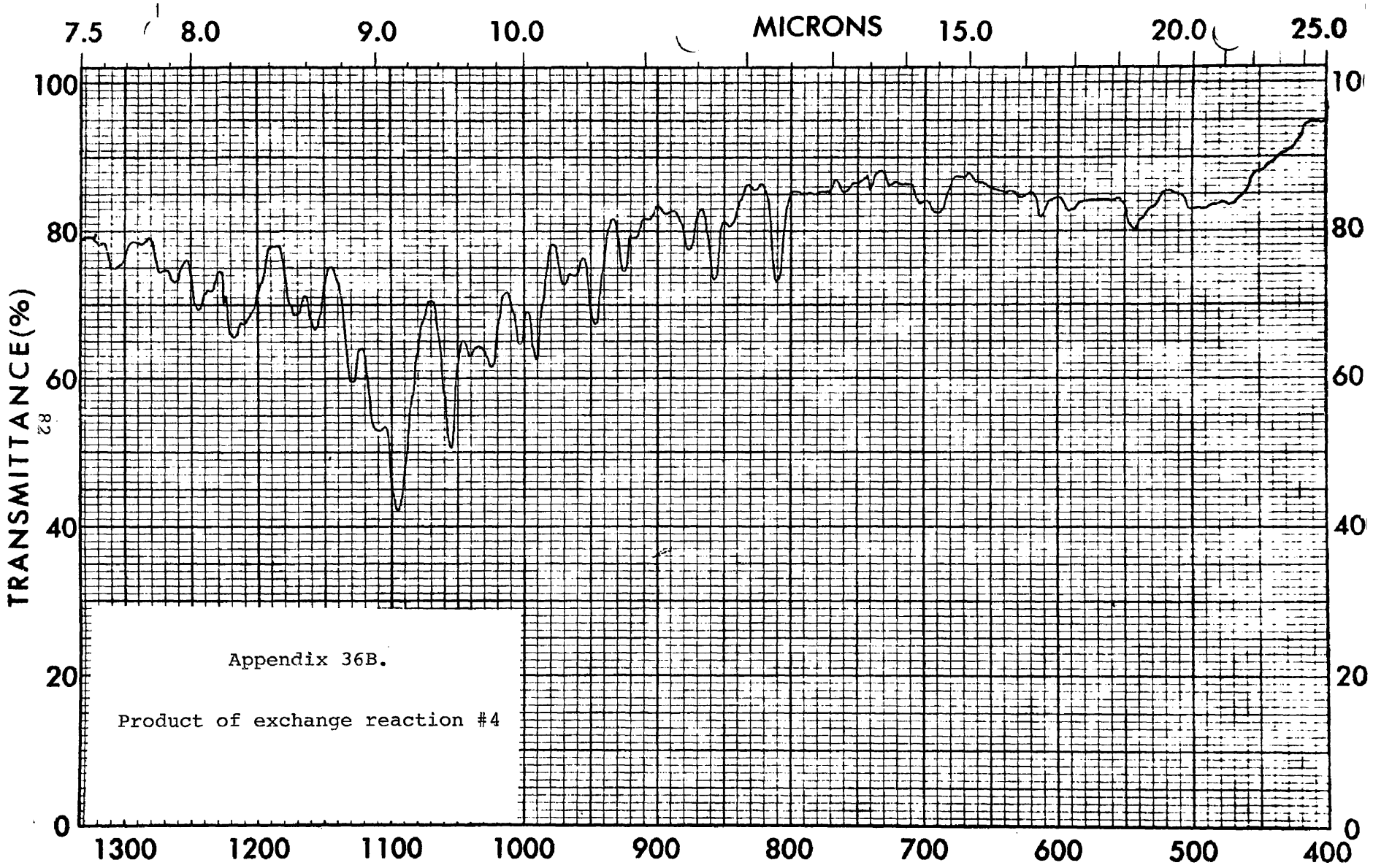
11α-Hydroxytestosterone (V)





Appendix 35A.

Product of exchange reaction #4

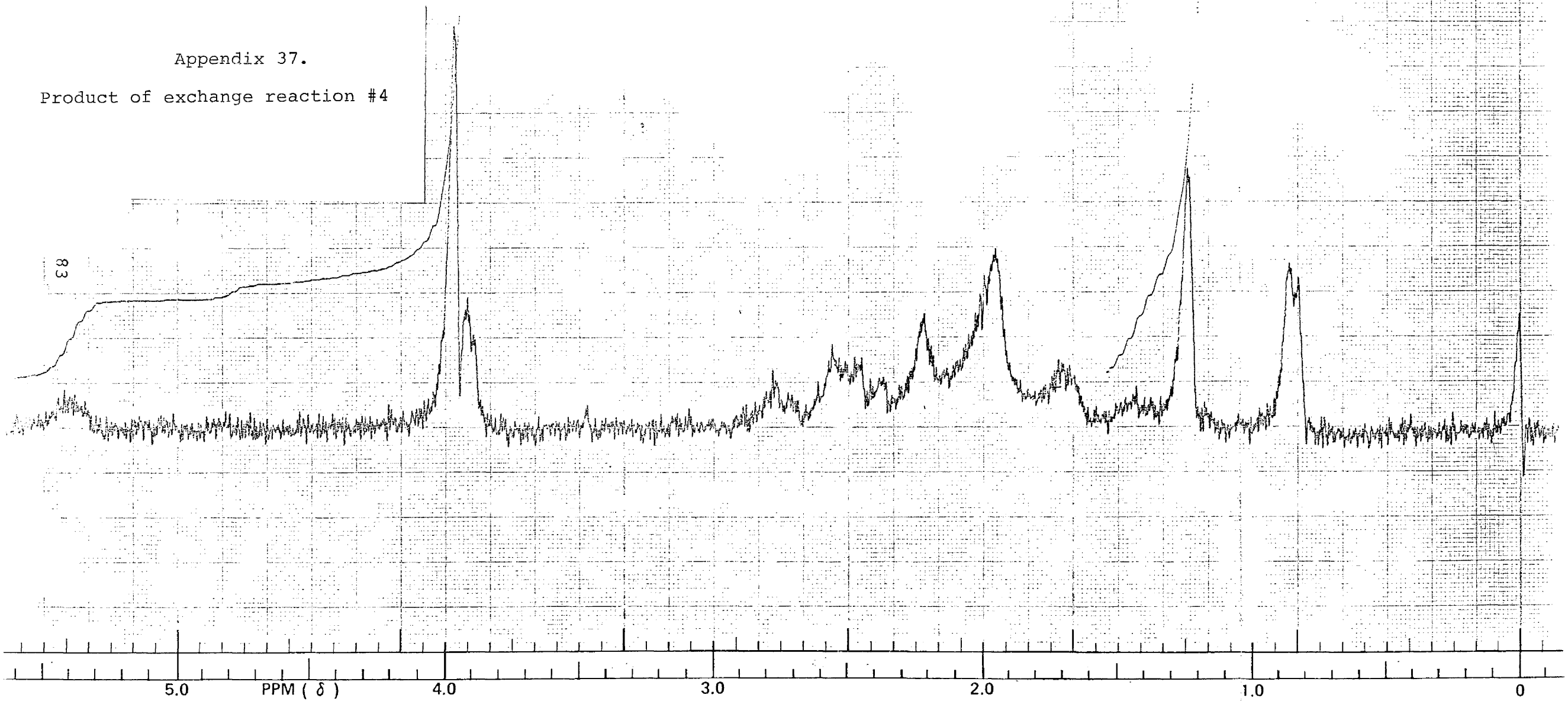


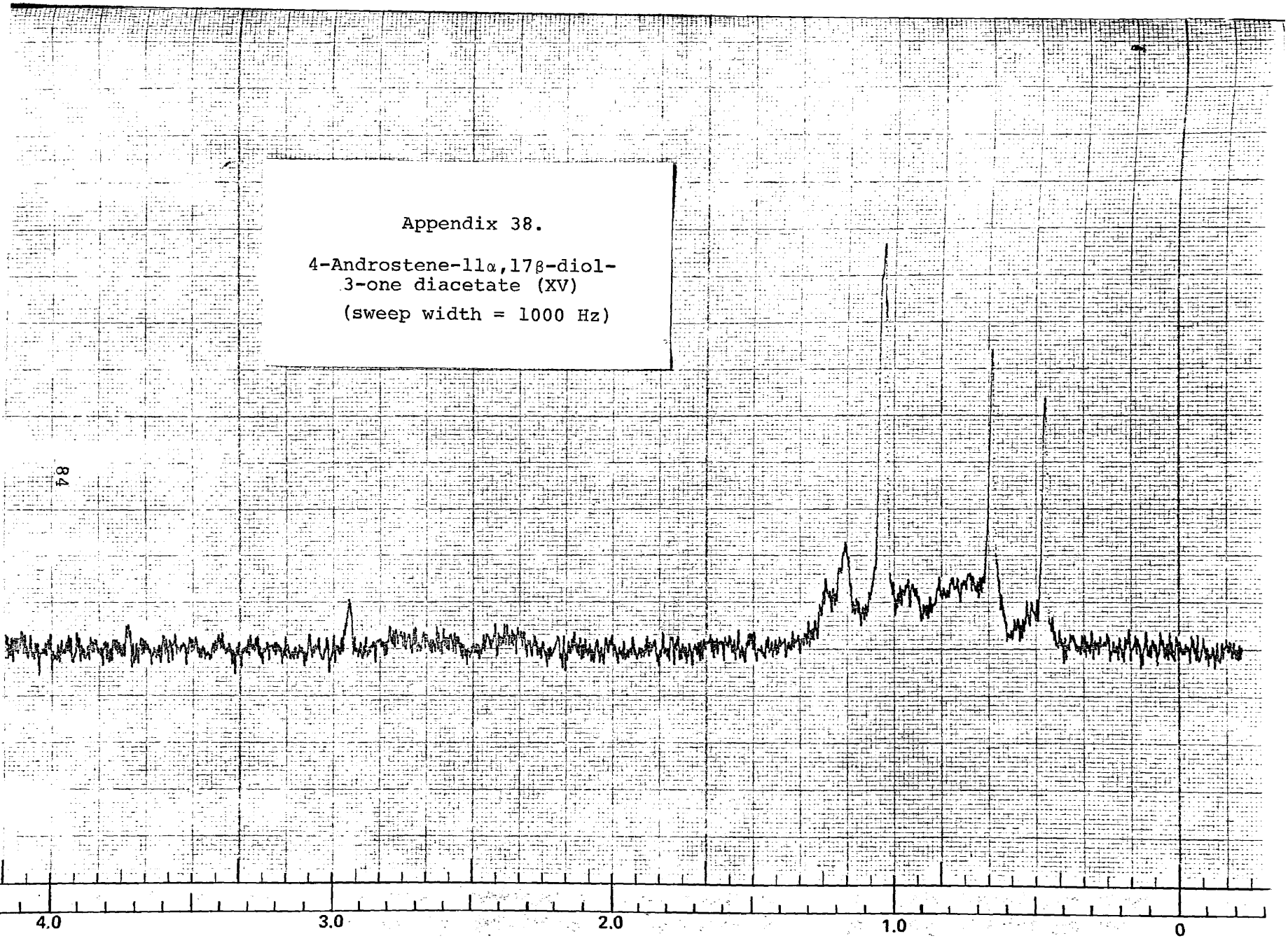
Appendix 36B.

Product of exchange reaction #4

Appendix 37.

Product of exchange reaction #4




Appendix 38.
4-Androstene-11α,17β-diol-
3-one diacetate (XV)
(sweep width = 1000 Hz)
84
4.0
3.0
2.0
1.0
0

Appendix 39.

4-Androstene-11α,17β-diol-
3-one diacetate (XV)